US009278767B2

(12) **United States Patent**
Meckstroth et al.

(10) **Patent No.: US 9,278,767 B2**
(45) **Date of Patent: Mar. 8, 2016**

(54) **DIRECT FILL DRY POWDER SYSTEMS WITH DOSING HEADS CONFIGURED FOR ON/OFF CONTROLLED FLOW**

(71) Applicant: **Oriel Therapeutics, Inc.**, Durham, NC (US)

(72) Inventors: **James R. Meckstroth**, Cary, NC (US); **Anthony James Hickey**, Chapel Hill, NC (US)

(73) Assignee: **Oriel Therapeutics, Inc.**, Durham, NC (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 139 days.

(21) Appl. No.: **14/221,648**

(22) Filed: **Mar. 21, 2014**

(65) **Prior Publication Data**

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Related U.S. Application Data

(62) Division of application No. 13/029,356, filed on Feb. 17, 2011, now Pat. No. 8,720,497.

(60) Provisional application No. 61/306,291, filed on Feb. 19, 2010.

(51) **Int. Cl.**
B65B 1/22 (2006.01)
B65B 1/08 (2006.01)
(Continued)

(52) **U.S. Cl.**
CPC ... ***B65B 1/22*** (2013.01); ***B65B 1/08*** (2013.01); ***B65B 1/363*** (2013.01); ***B65B 39/00*** (2013.01); ***B65D 88/66*** (2013.01); *B65B 37/04* (2013.01); *B65B 2039/009* (2013.01)

(58) **Field of Classification Search**
CPC B65B 1/20; B65B 1/22; B65D 88/54; B65D 88/64; B65D 88/66
USPC 141/72; 222/161, 196; 128/203.15
See application file for complete search history.

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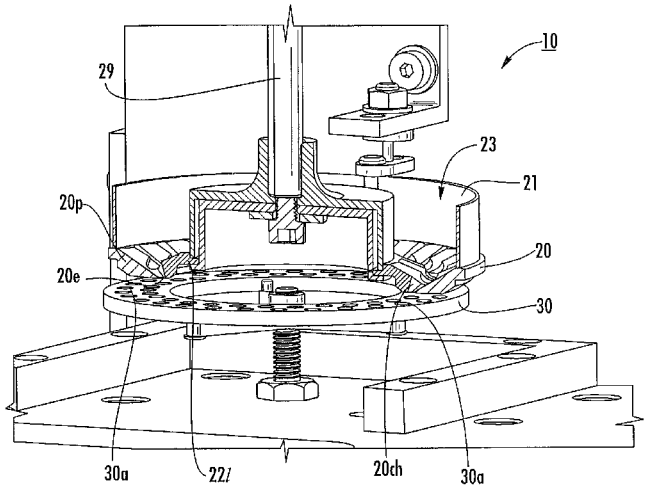
Primary Examiner — Timothy L Maust
(74) *Attorney, Agent, or Firm* — Myers Bigel & Sibley, P.A.

(57) **ABSTRACT**

Apparatus for dispensing a defined amount of dry powder concurrently to a plurality of spaced apart dose receiving containers include: (a) a dosing head comprising a support body with a plurality of spaced apart elongate channels having a channel length with an upper end defining an entry orifice and a lower end defining an exit port; (b) a dry powder bed residing above and in communication with the dosing head; and (c) at least one vibration source in communication with the dosing head channels configured to controllably apply a vibration flow signal, wherein, when the vibration flow signal is applied to the dosing head channels, dry powder from the dry powder bed flows through the elongate channels and out the exit port and when the flow signal is removed, dry powder does not flow through the dosing head elongate channels.

15 Claims, 34 Drawing Sheets



(51) **Int. Cl.**

B65B 39/00	(2006.01)
B65B 1/36	(2006.01)
B65D 88/66	(2006.01)
B65B 37/04	(2006.01)

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2009/0014086	A1 *	1/2009	MacMichael	B65B 1/08 141/12

* cited by examiner

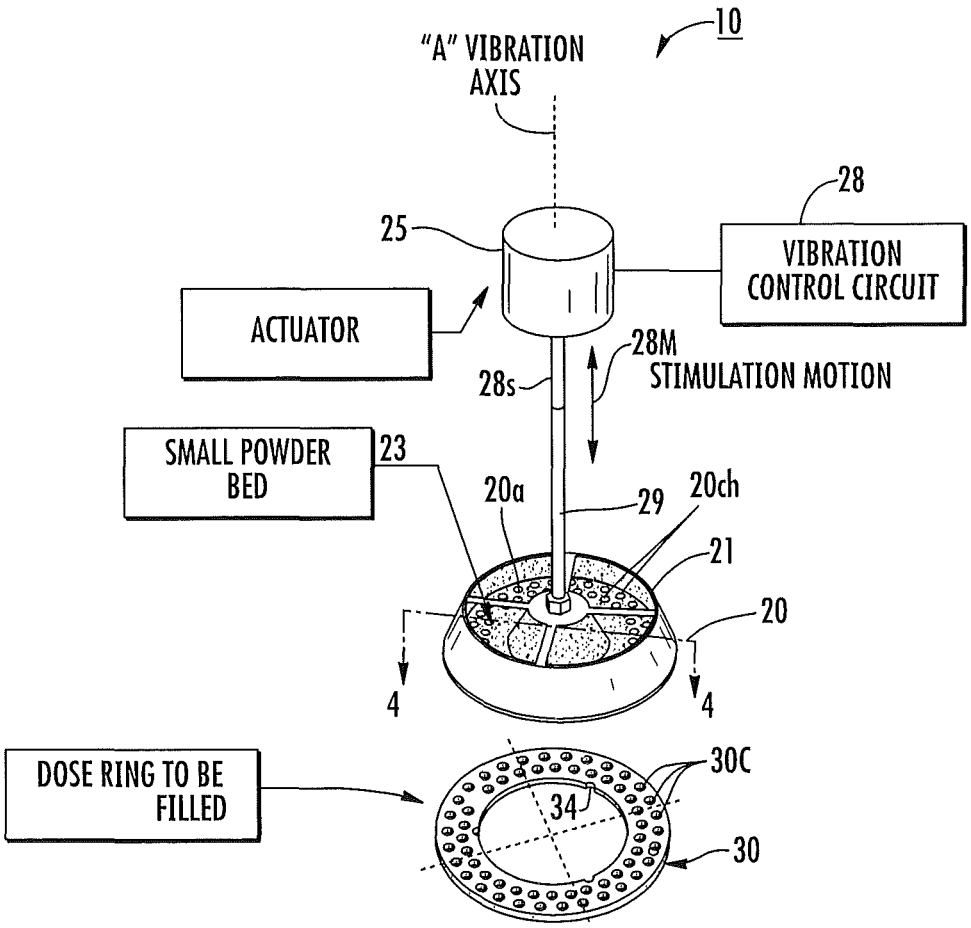

10
"A" VIBRATION AXIS
28
25
VIBRATION CONTROL CIRCUIT
ACTUATOR
28M
28s
STIMULATION MOTION
SMALL POWDER BED
23
20a
29
20ch
21
20
4
4
DOSE RING TO BE FILLED
30C
34
30

FIG. 1

FIG. 2A

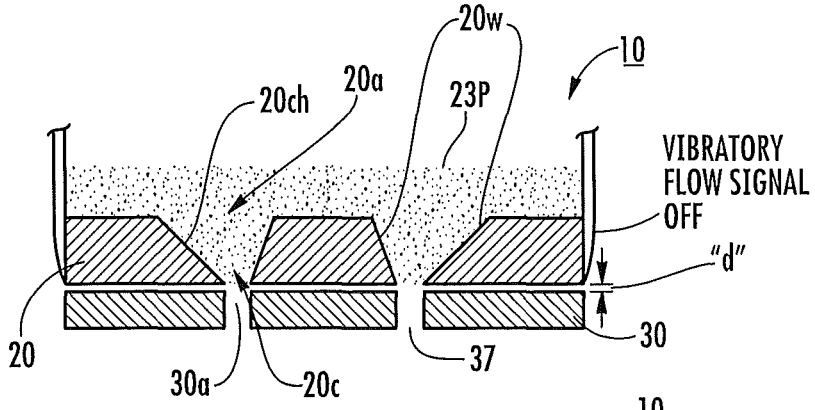
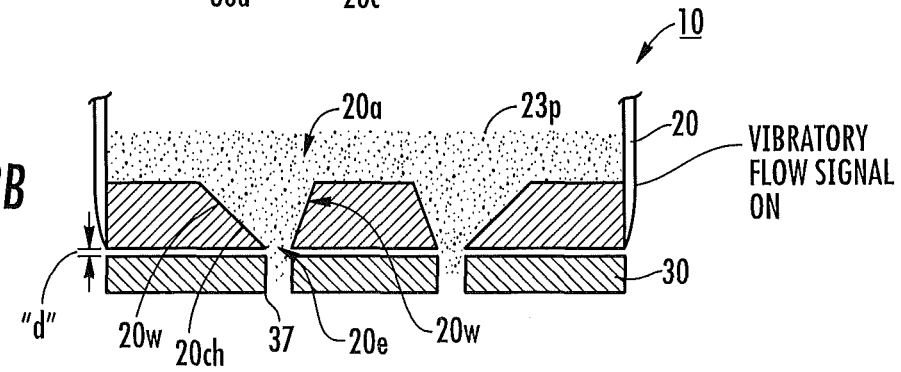

20w
10
20ch
20a
23P
VIBRATORY
FLOW SIGNAL
OFF
"d"
20
30a
20c
37
30

FIG. 2B


10
20a
23p
20
VIBRATORY
FLOW SIGNAL
ON
30
"d"
20w
20ch
37
20e
20w

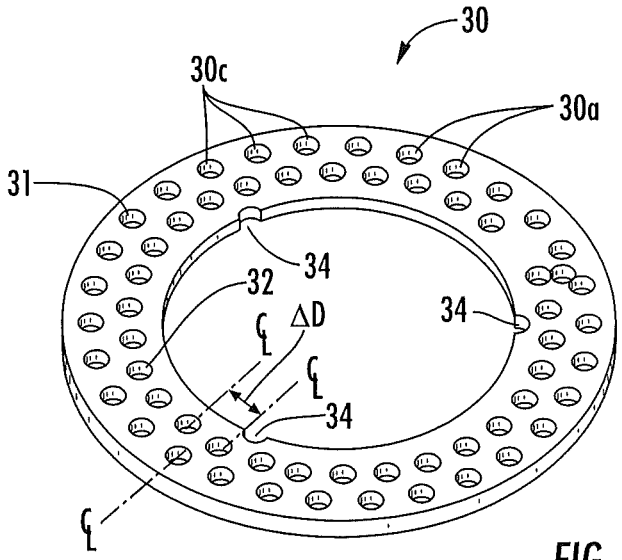


FIG. 3A

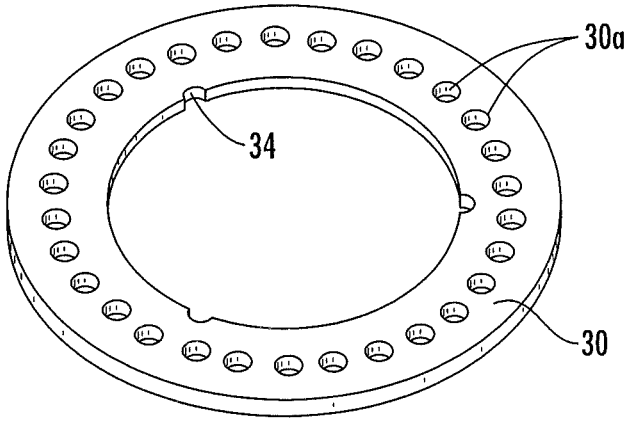


FIG. 3B

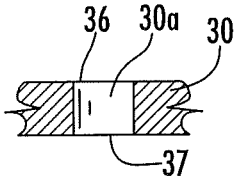


FIG. 3C

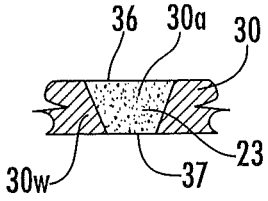


FIG. 3D

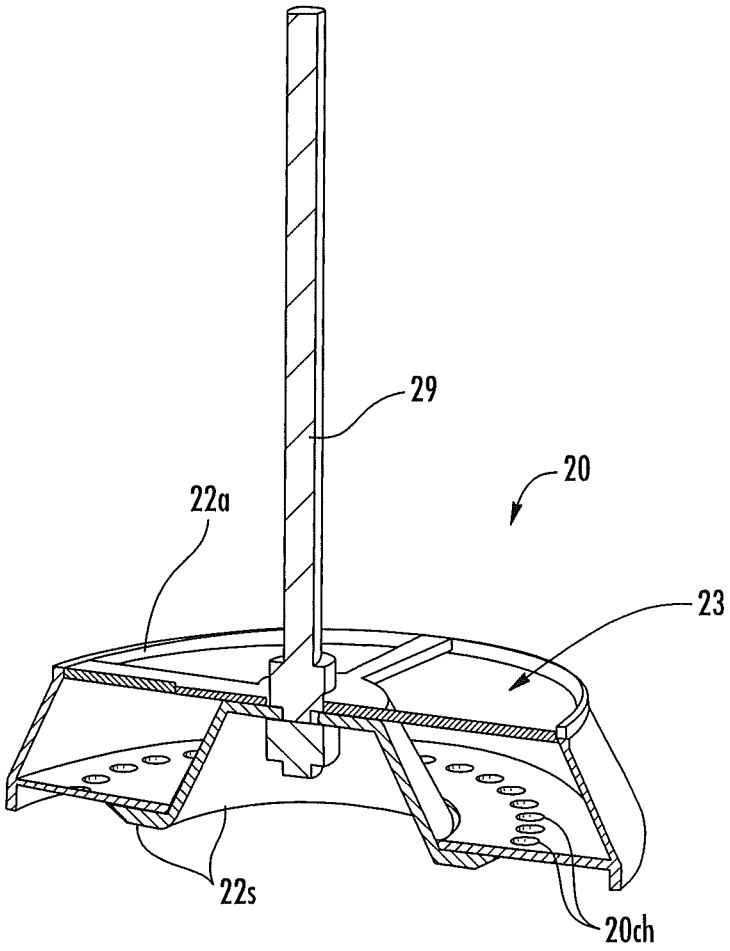


FIG. 4

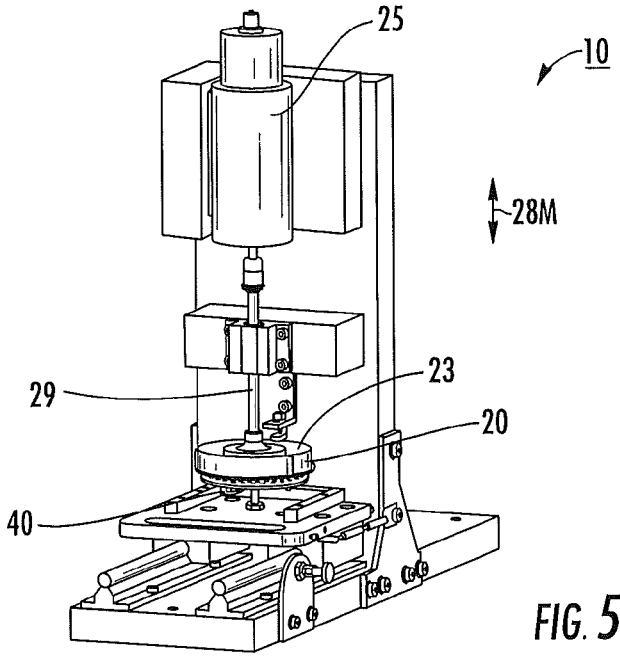


FIG. 5A

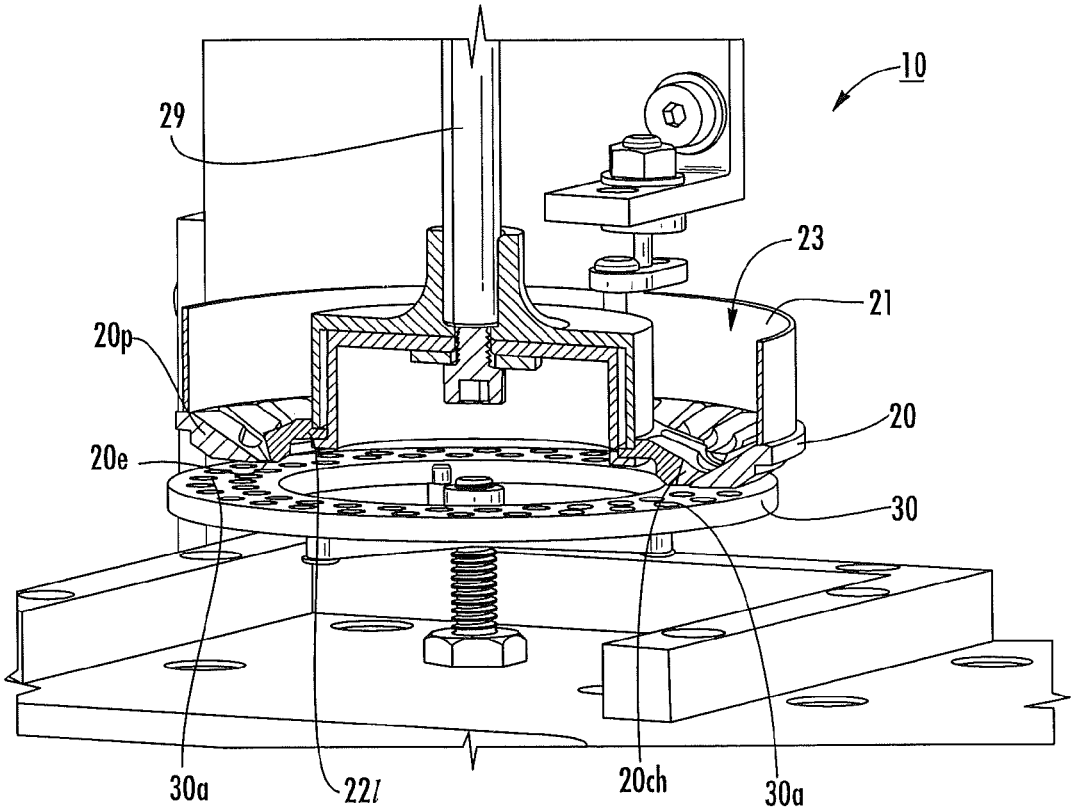


FIG. 5B

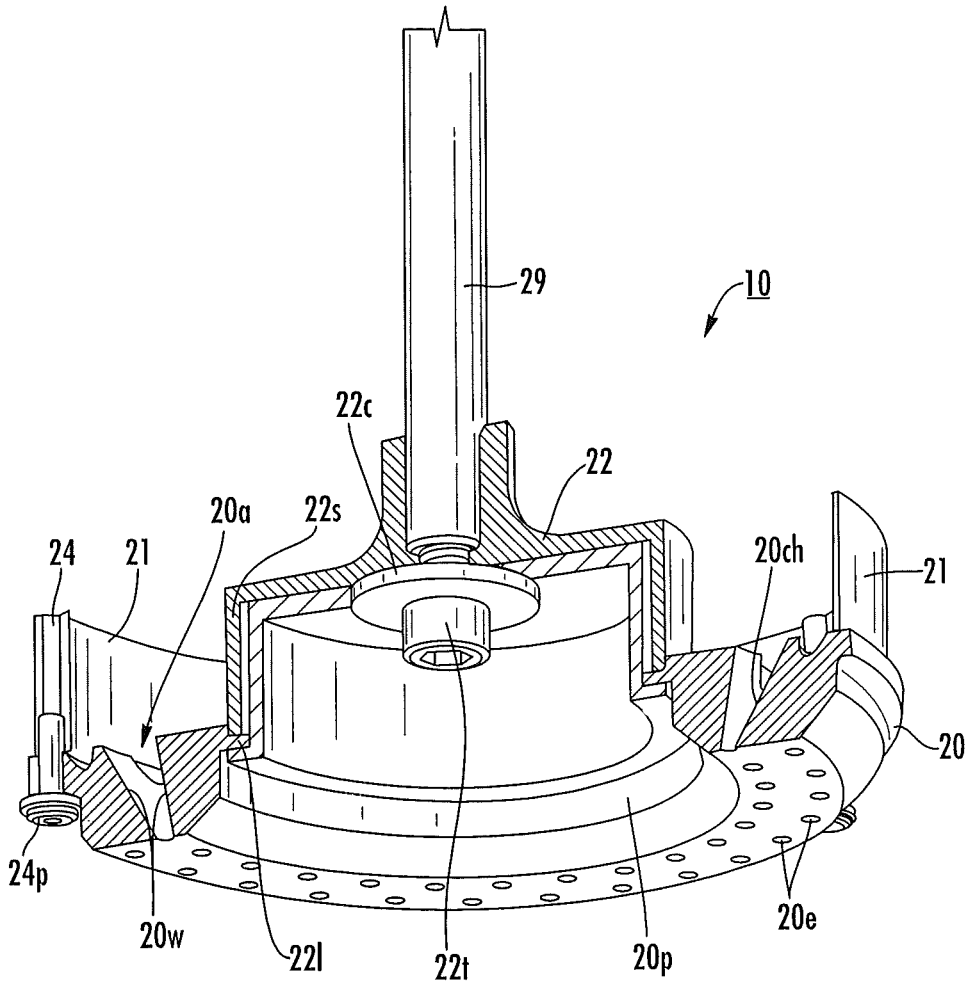


FIG. 5C

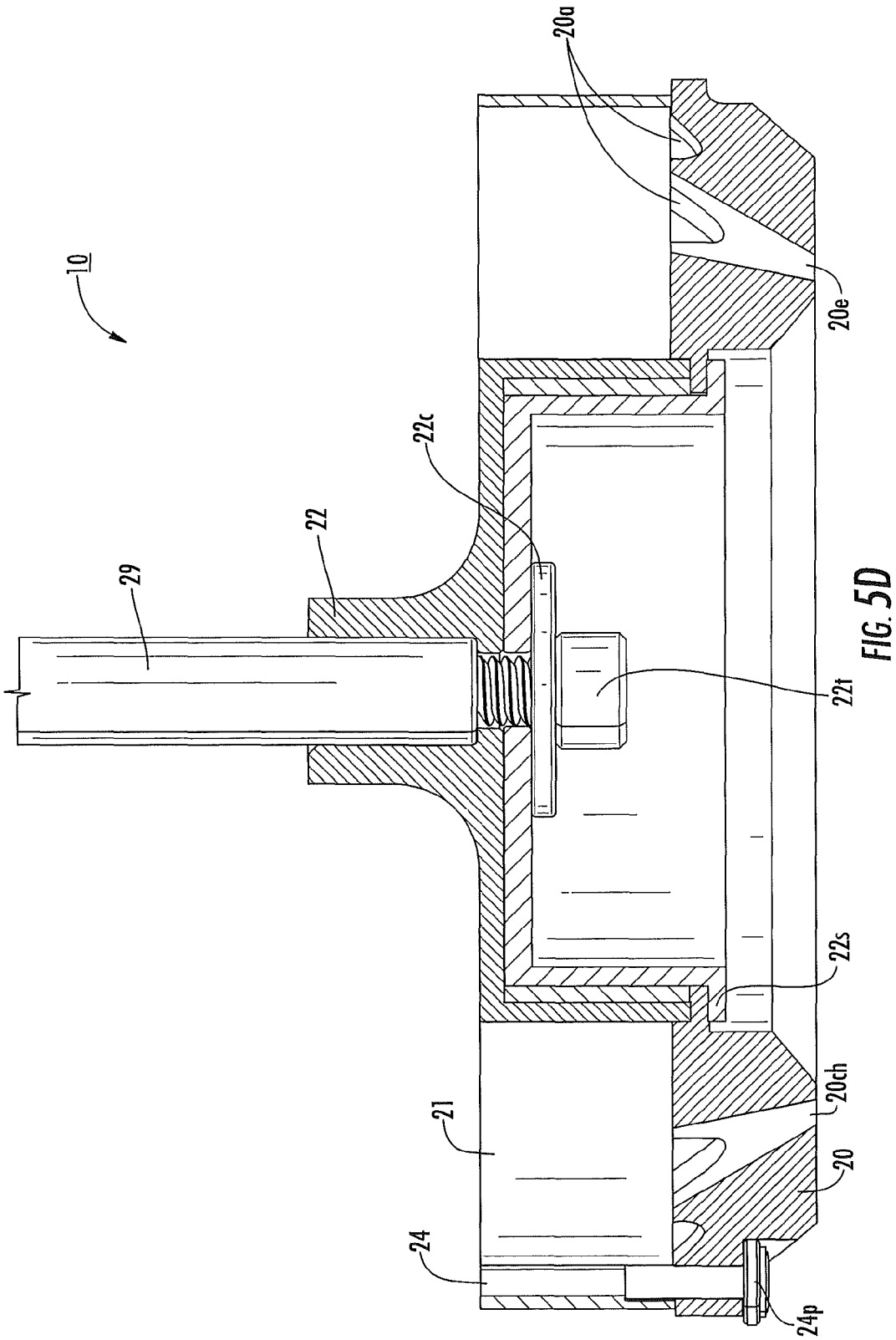


FIG. 5D

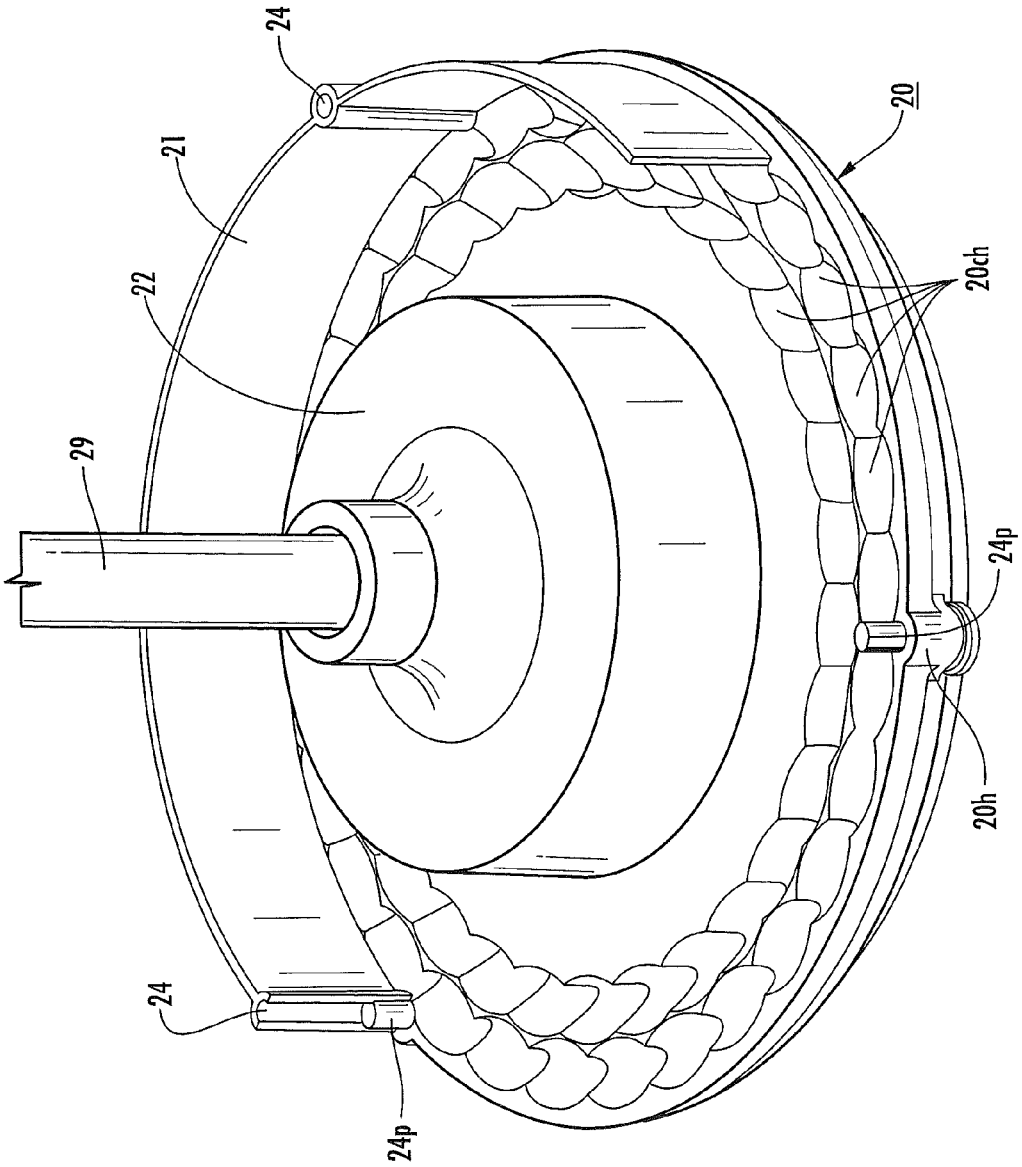


FIG. 5E

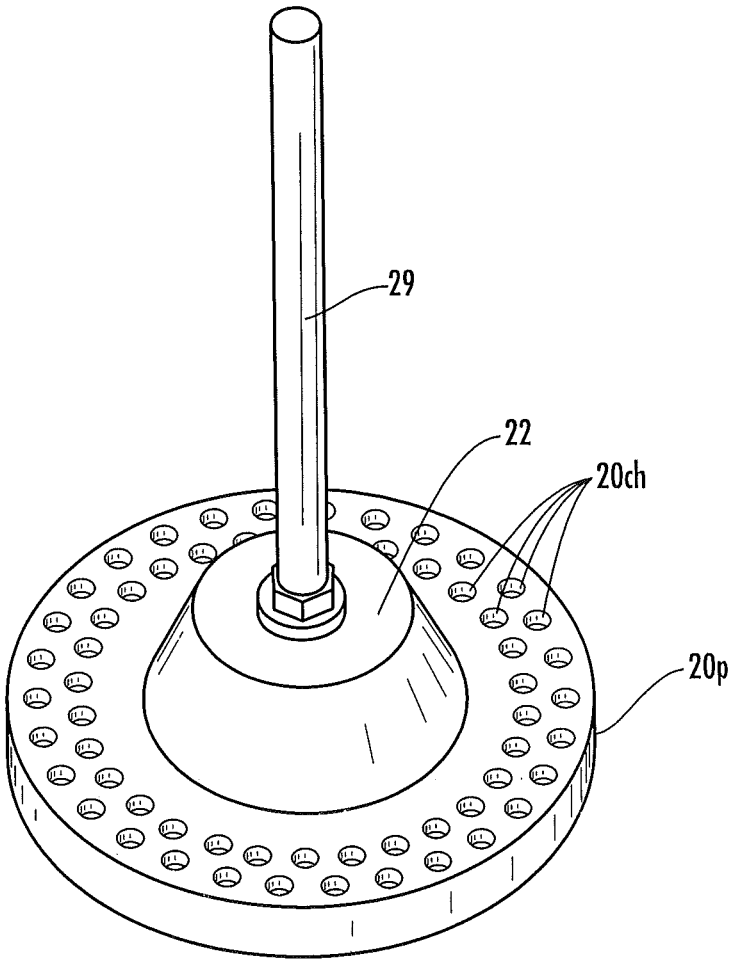


FIG. 6

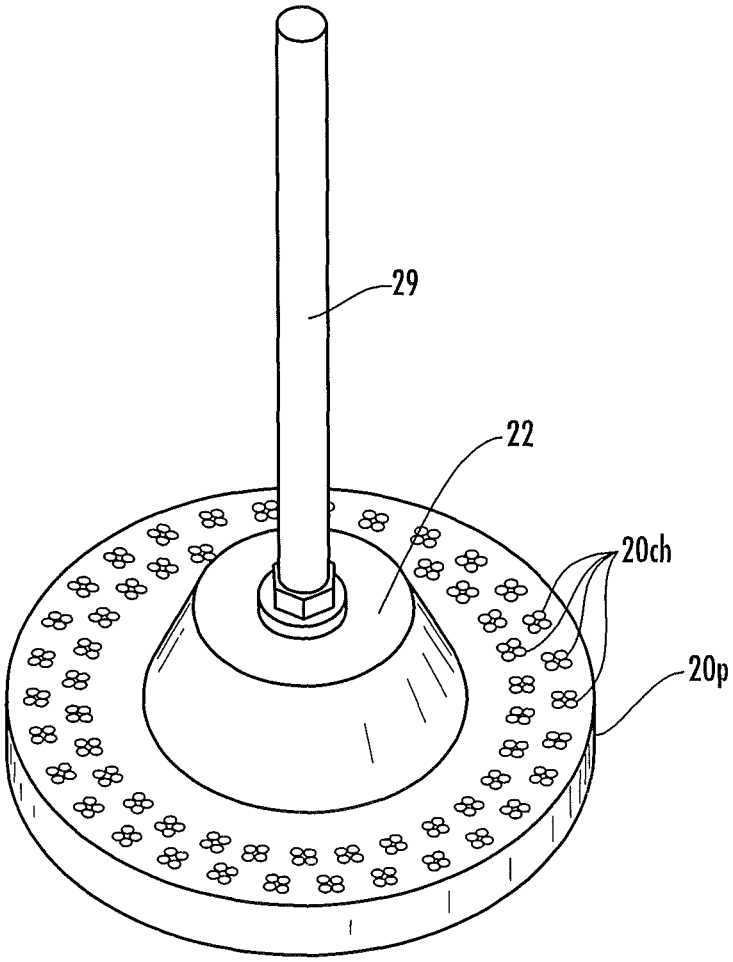


FIG. 7

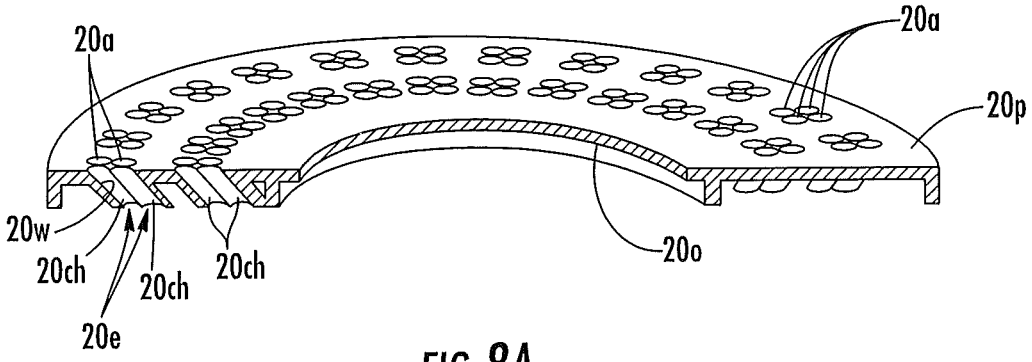


FIG. 8A

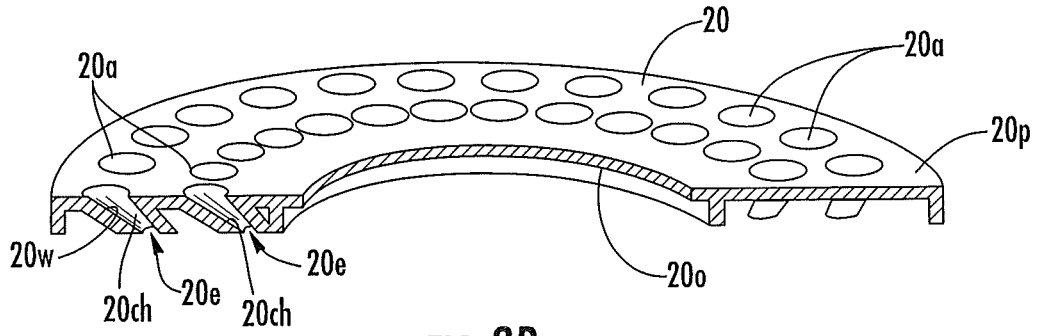


FIG. 8B

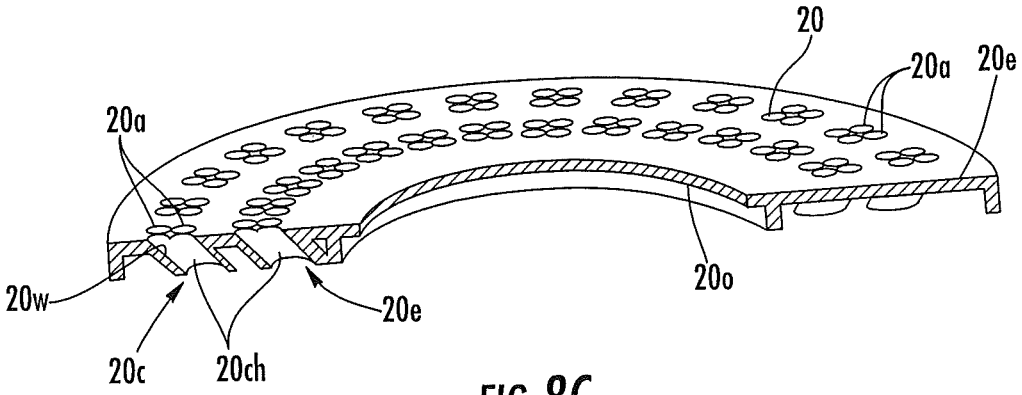


FIG. 8C

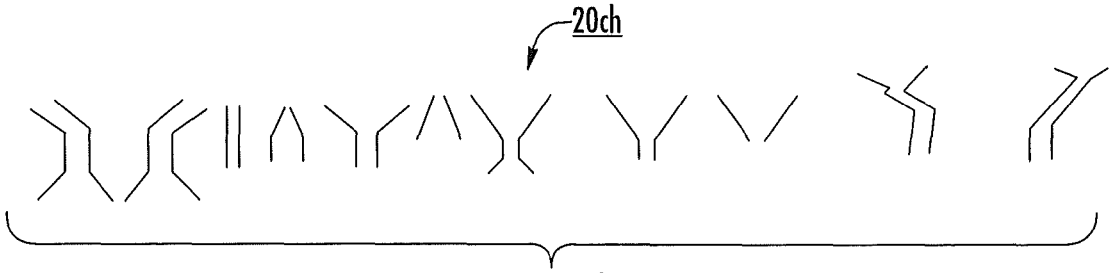


FIG. 10

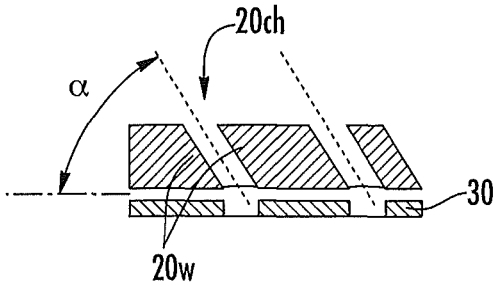


FIG. 9B

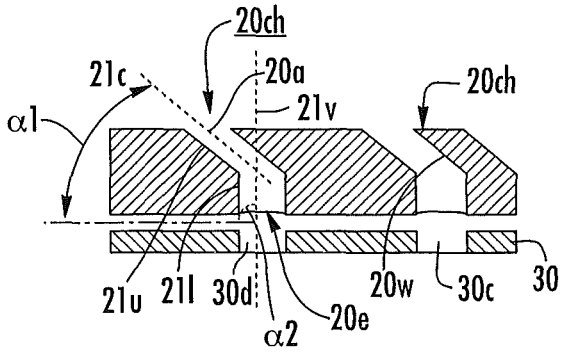


FIG. 9A

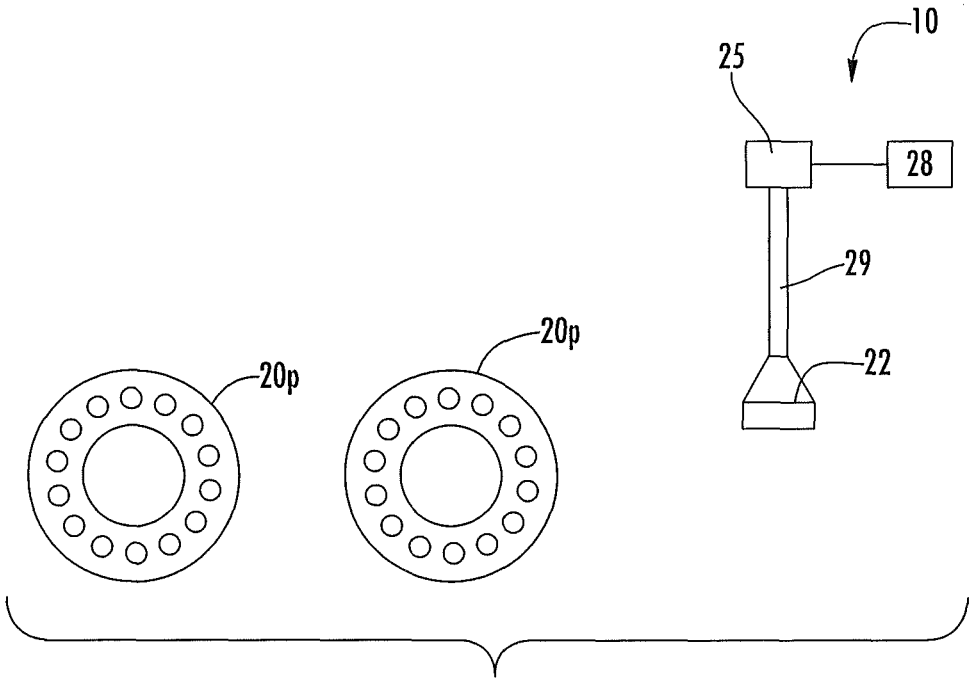


FIG. 11

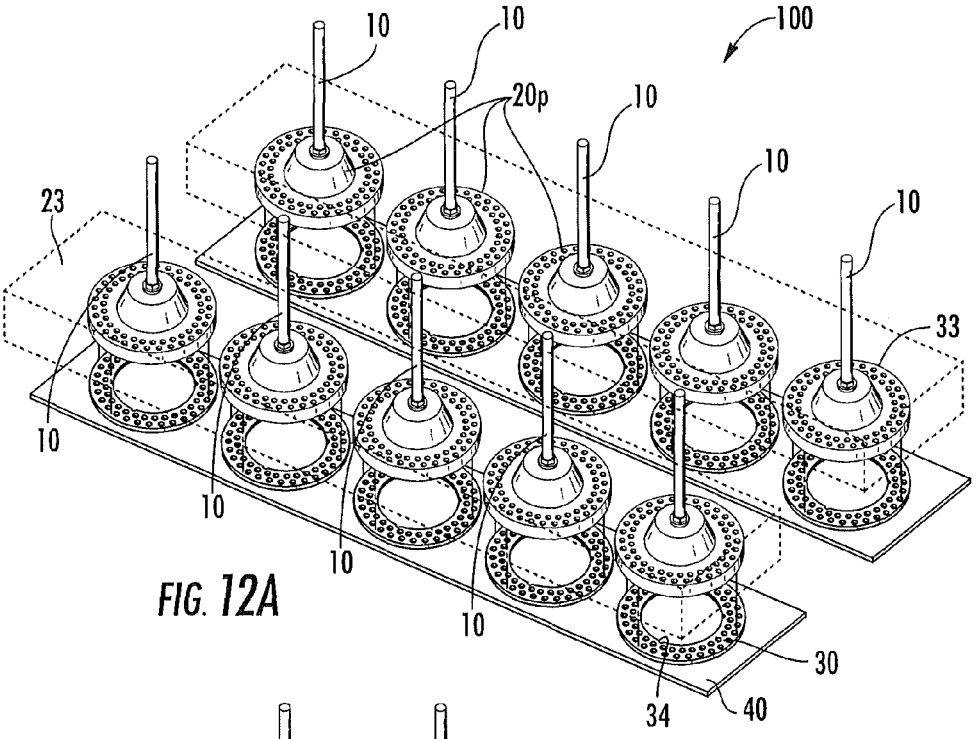


FIG. 12A

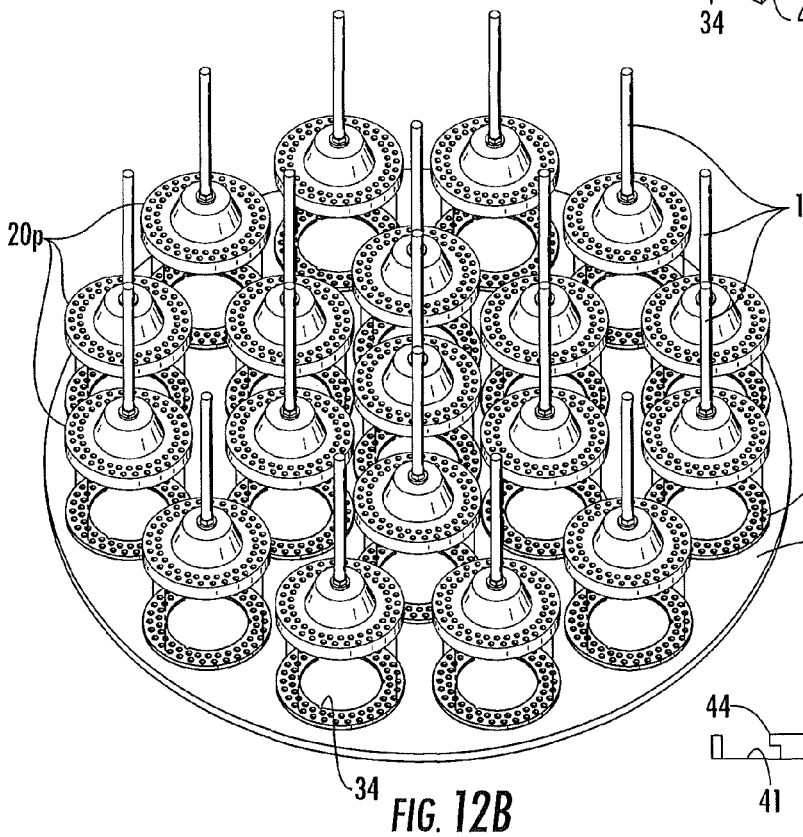


FIG. 12B

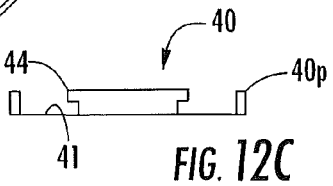


FIG. 12C

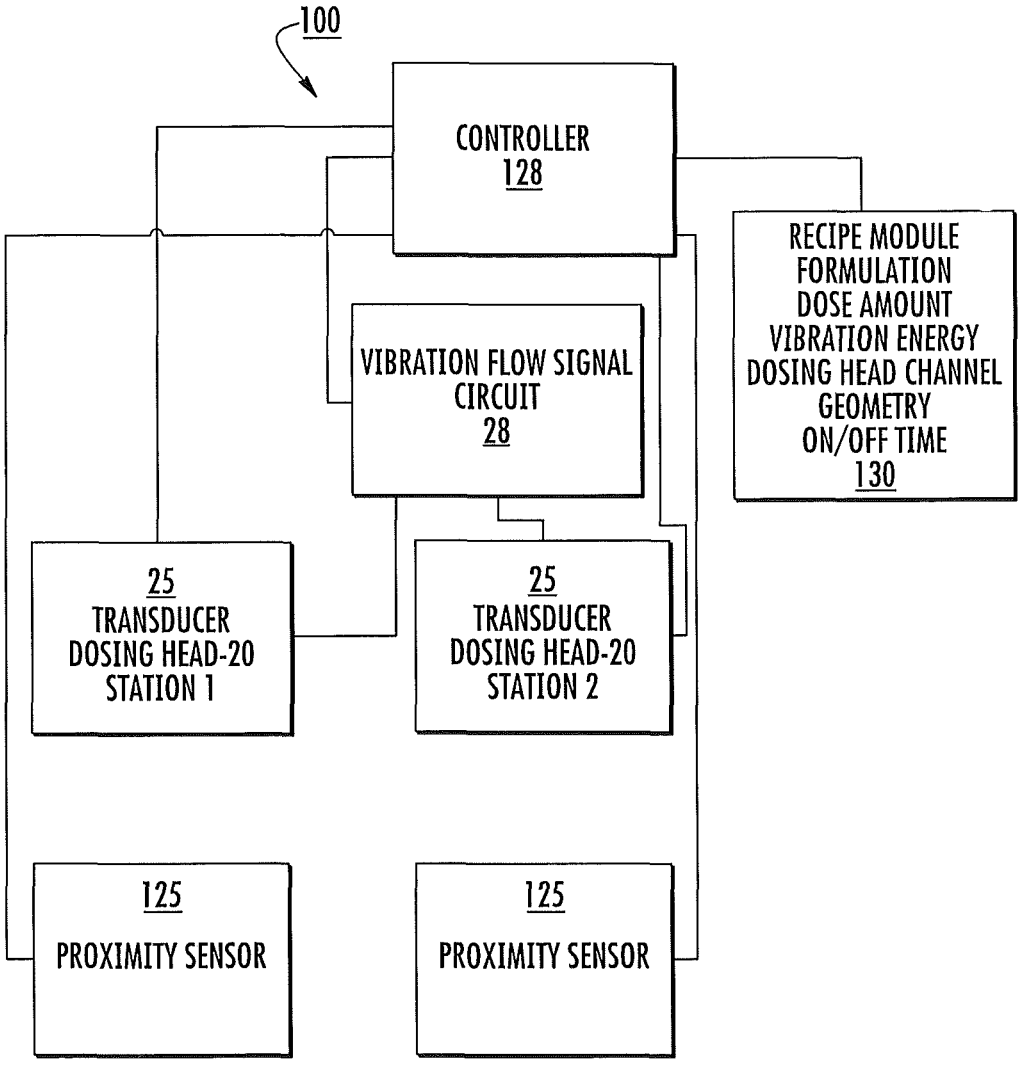

100
CONTROLLER
128
RECIPE MODULE
FORMULATION
DOSE AMOUNT
VIBRATION ENERGY
DOSING HEAD CHANNEL
GEOMETRY
ON/OFF TIME
130
VIBRATION FLOW SIGNAL
CIRCUIT
28
25
TRANSDUCER
DOSING HEAD-20
STATION 1
25
TRANSDUCER
DOSING HEAD-20
STATION 2
125
PROXIMITY SENSOR
125
PROXIMITY SENSOR

FIG. 13

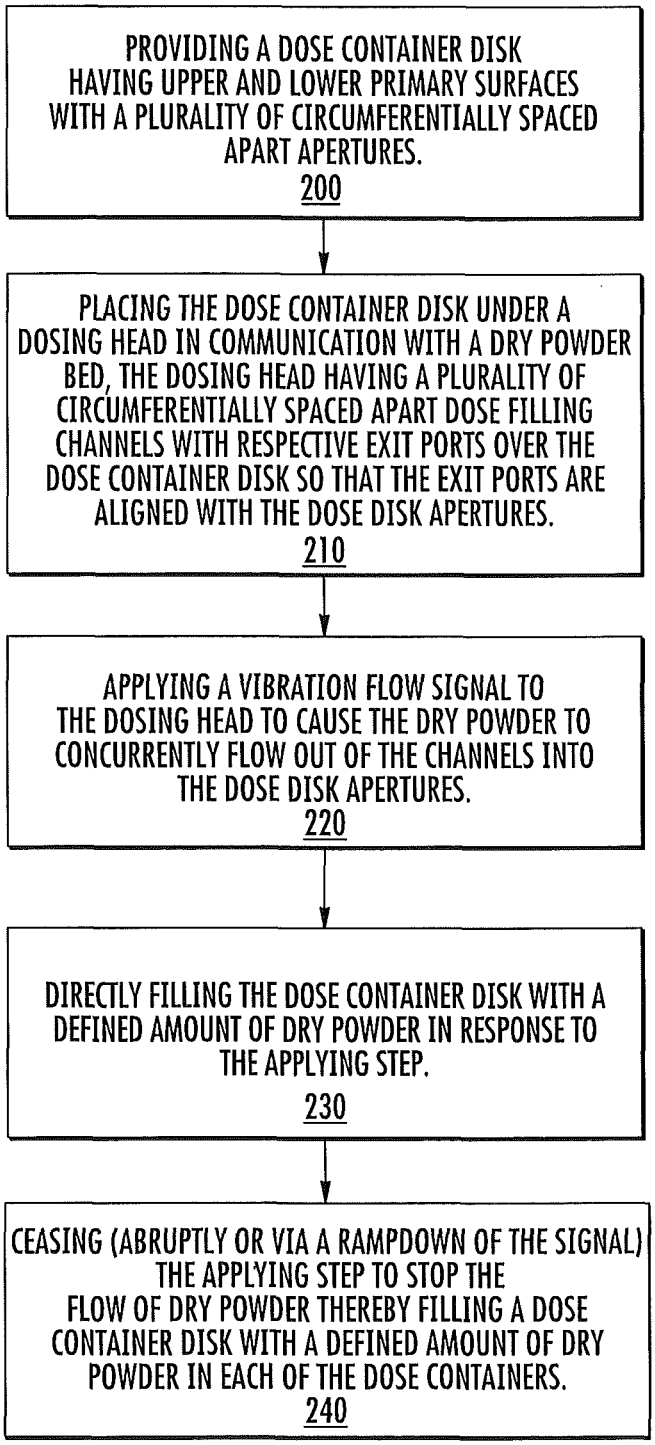

PROVIDING A DOSE CONTAINER DISK HAVING UPPER AND LOWER PRIMARY SURFACES WITH A PLURALITY OF CIRCUMFERENTIALLY SPACED APART APERTURES.
200
PLACING THE DOSE CONTAINER DISK UNDER A DOSING HEAD IN COMMUNICATION WITH A DRY POWDER BED, THE DOSING HEAD HAVING A PLURALITY OF CIRCUMFERENTIALLY SPACED APART DOSE FILLING CHANNELS WITH RESPECTIVE EXIT PORTS OVER THE DOSE CONTAINER DISK SO THAT THE EXIT PORTS ARE ALIGNED WITH THE DOSE DISK APERTURES.
210
APPLYING A VIBRATION FLOW SIGNAL TO THE DOSING HEAD TO CAUSE THE DRY POWDER TO CONCURRENTLY FLOW OUT OF THE CHANNELS INTO THE DOSE DISK APERTURES.
220
DIRECTLY FILLING THE DOSE CONTAINER DISK WITH A DEFINED AMOUNT OF DRY POWDER IN RESPONSE TO THE APPLYING STEP.
230
CEASING (ABRUPTLY OR VIA A RAMPDOWN OF THE SIGNAL) THE APPLYING STEP TO STOP THE FLOW OF DRY POWDER THEREBY FILLING A DOSE CONTAINER DISK WITH A DEFINED AMOUNT OF DRY POWDER IN EACH OF THE DOSE CONTAINERS.
240

FIG. 14

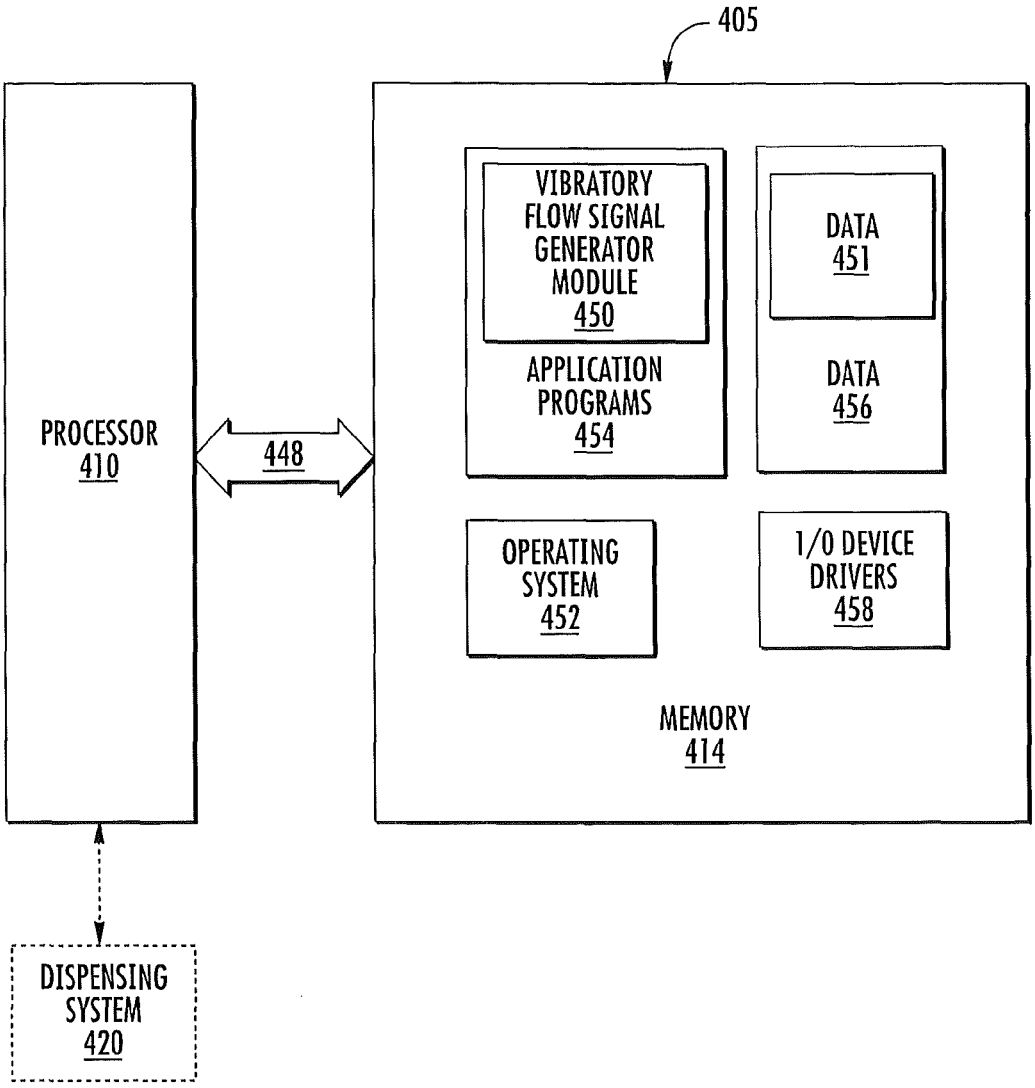

405
PROCESSOR
410
448
VIBRATORY
FLOW SIGNAL
GENERATOR
MODULE
450
APPLICATION
PROGRAMS
454
DATA
451
DATA
456
OPERATING
SYSTEM
452
1/0 DEVICE
DRIVERS
458
MEMORY
414
DISPENSING
SYSTEM
420

FIG. 15

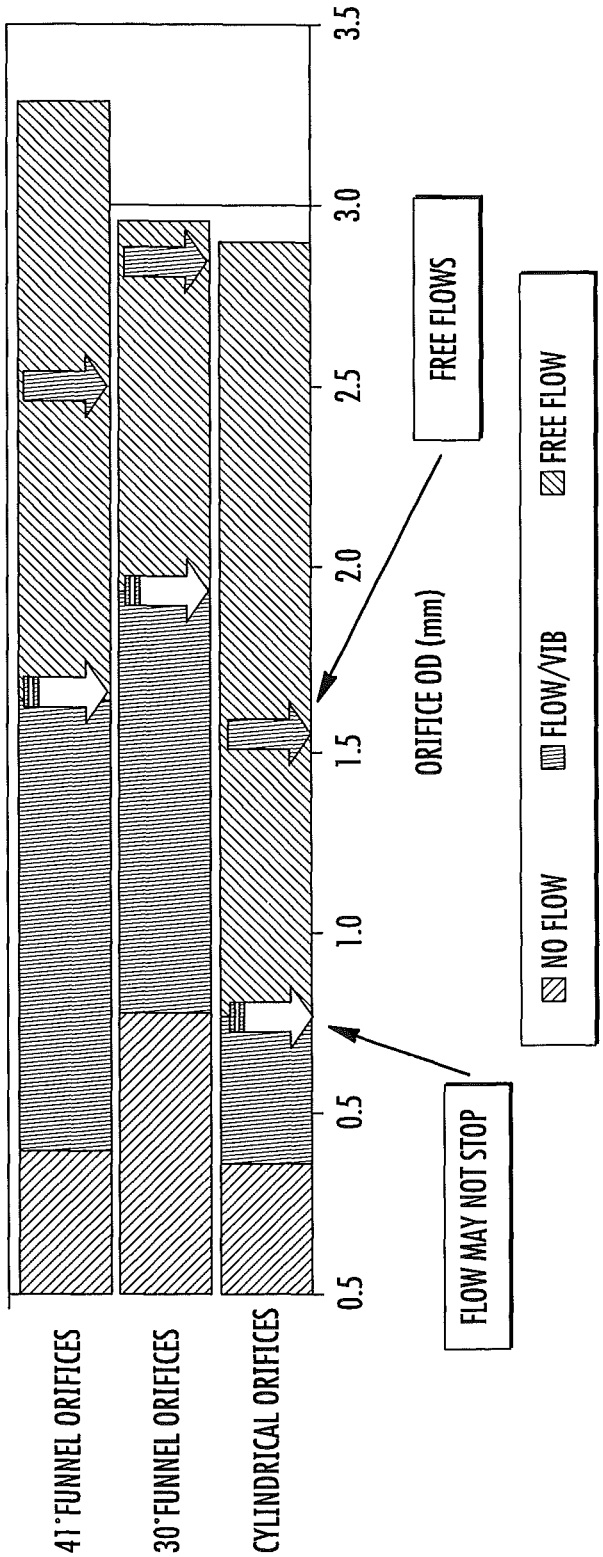

41°FUNNEL ORIFICES
30°FUNNEL ORIFICES
CYLINDRICAL ORIFICES
0.5
1.0
1.5
2.0
2.5
3.0
3.5
ORIFICE OD (mm)
FREE FLOWS
FLOW MAY NOT STOP
NO FLOW
FLOW/VIB
FREE FLOW

FIG. 16

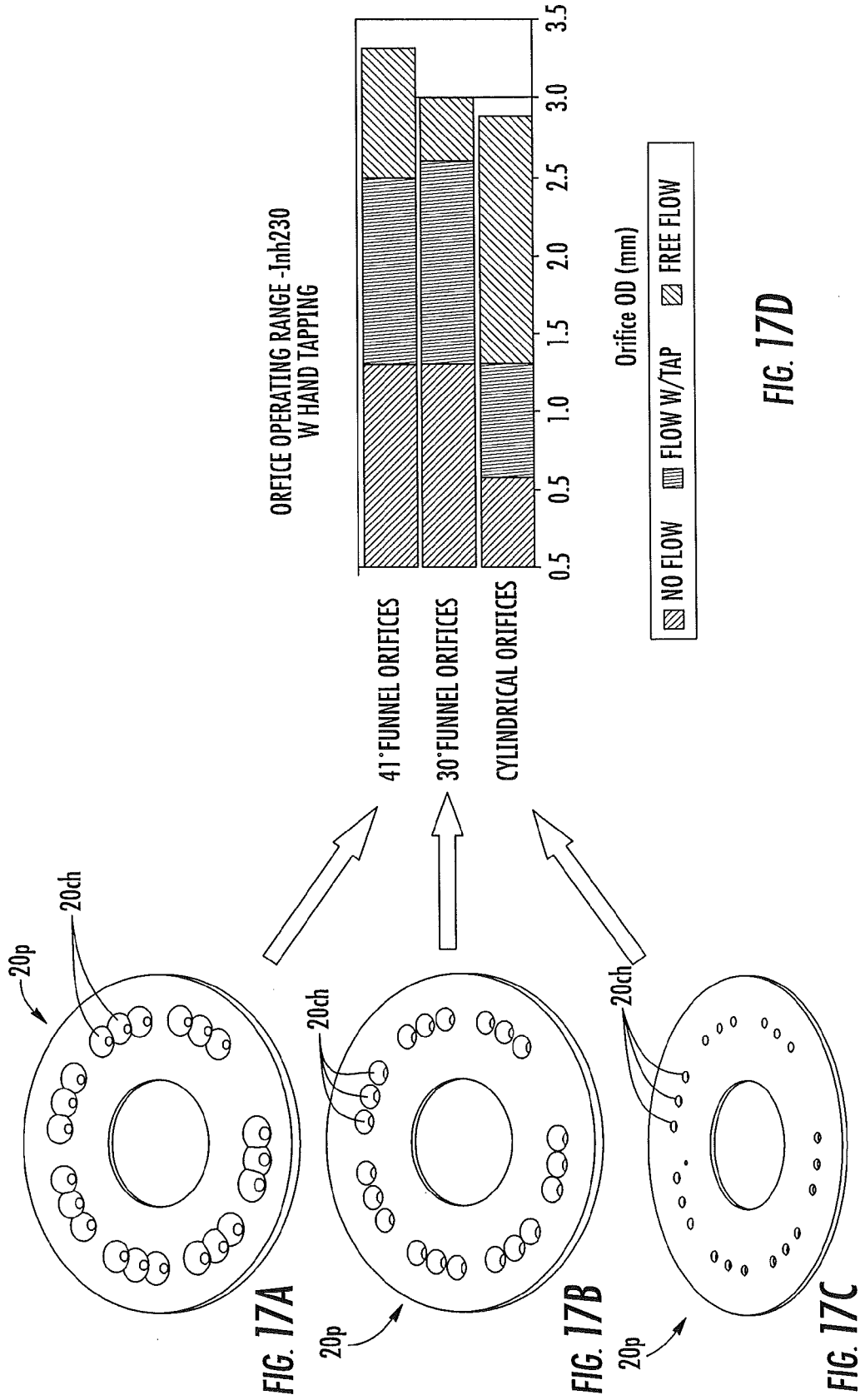


FIG. 17A

FIG. 17B

FIG. 17C

FIG. 17D

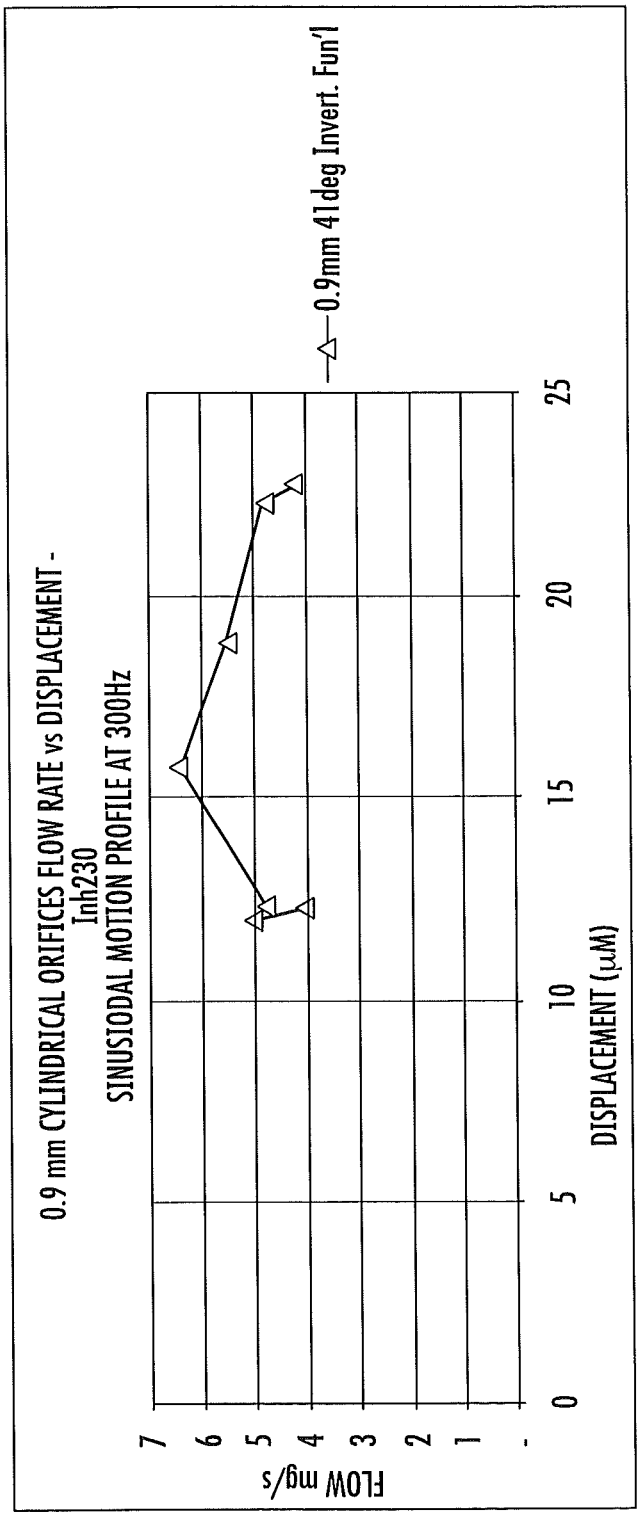

0.9 mm CYLINDRICAL ORIFICES FLOW RATE vs DISPLACEMENT -
Inh230
SINUSIODAL MOTION PROFILE AT 300Hz
0.9mm 41deg Invert. Fun'l
FLOW mg/s
DISPLACEMENT (μM)
0
5
10
15
20
25
1
2
3
4
5
6
7

FIG. 18

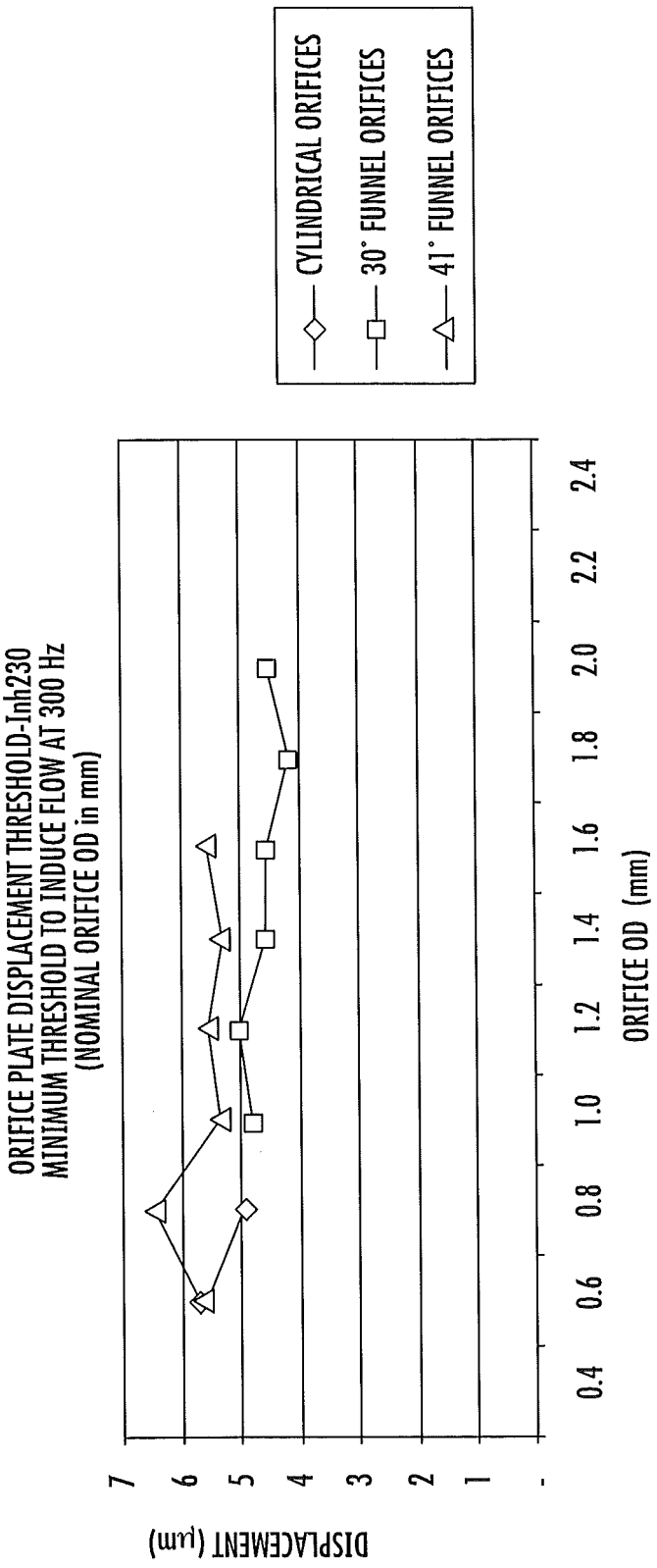

ORIFICE PLATE DISPLACEMENT THRESHOLD-Inh230
MINIMUM THRESHOLD TO INDUCE FLOW AT 300 Hz
(NOMINAL ORIFICE OD in mm)
CYLINDRICAL ORIFICES
30° FUNNEL ORIFICES
41° FUNNEL ORIFICES
DISPLACEMENT (μm)
7
6
5
4
3
2
1
-
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
ORIFICE OD (mm)

FIG. 19

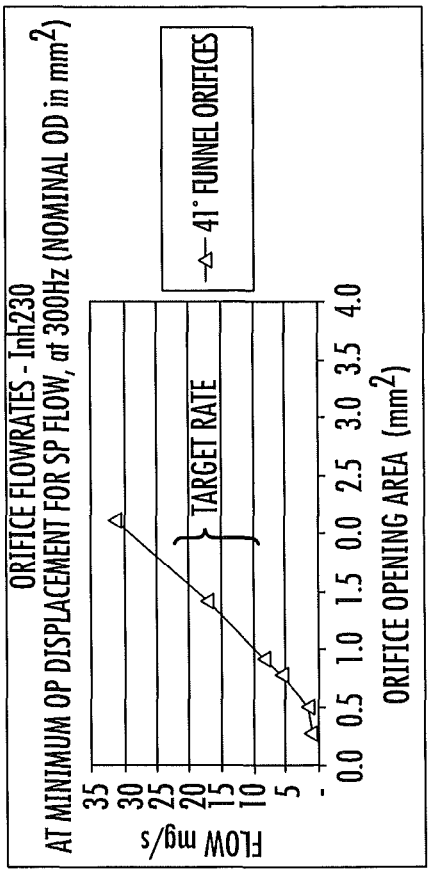


FIG. 20B

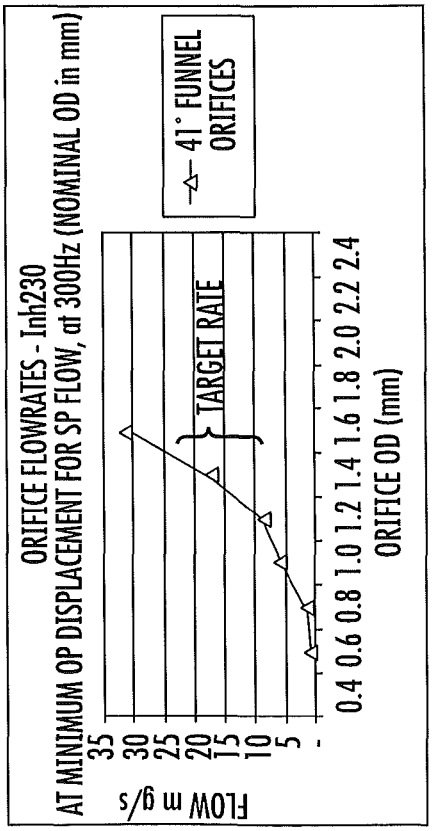


FIG. 20A

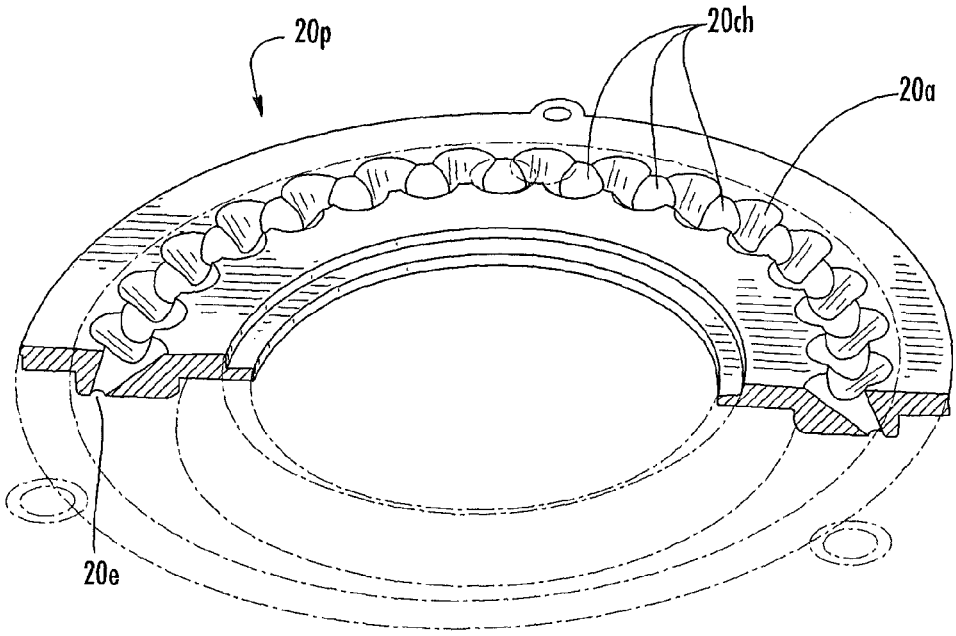


FIG. 21A

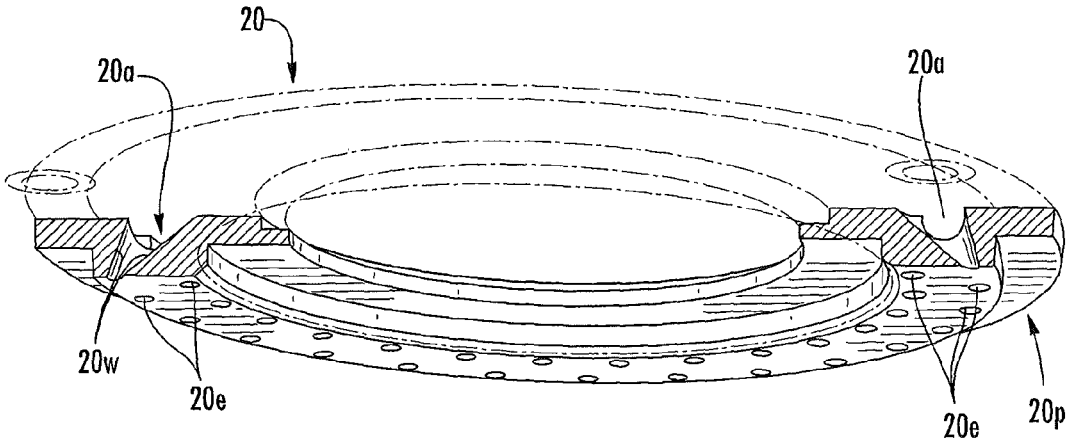


FIG. 21B

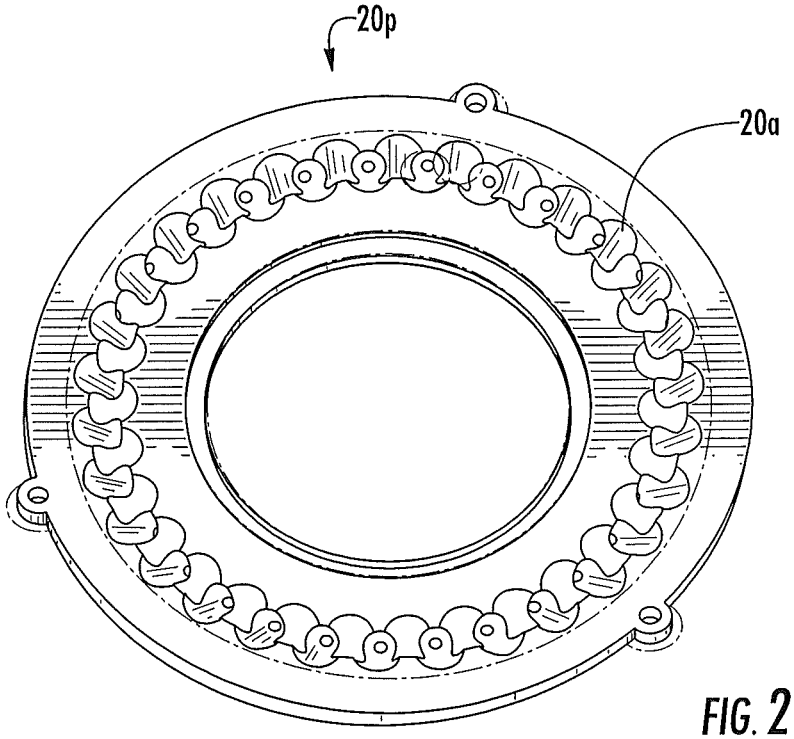


FIG. 21C

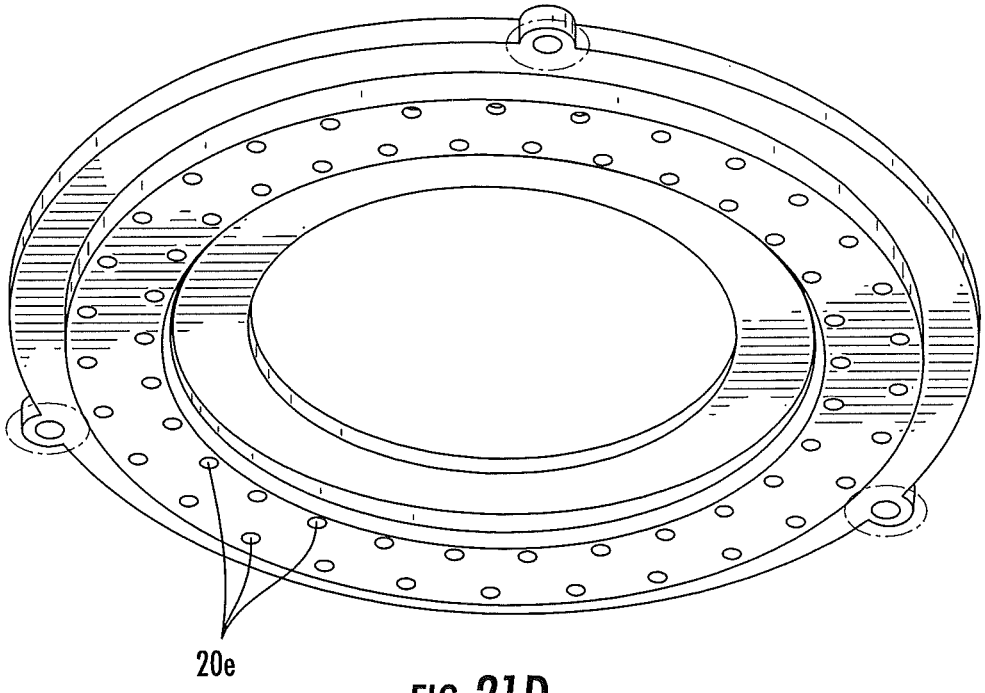


FIG. 21D

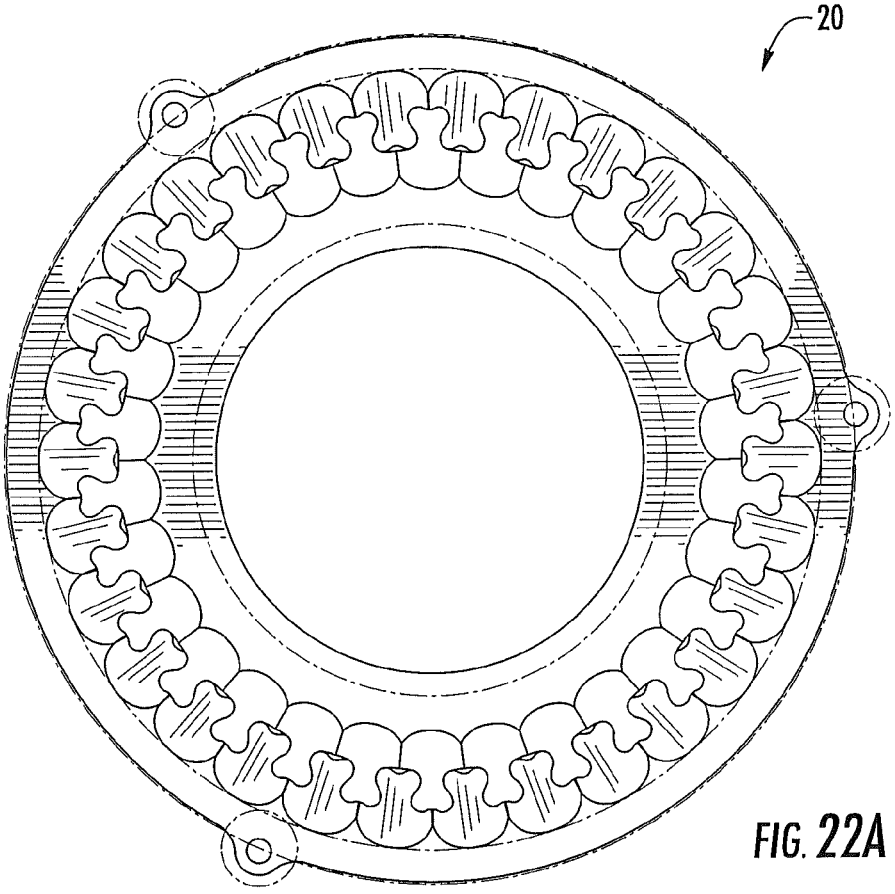


FIG. 22A

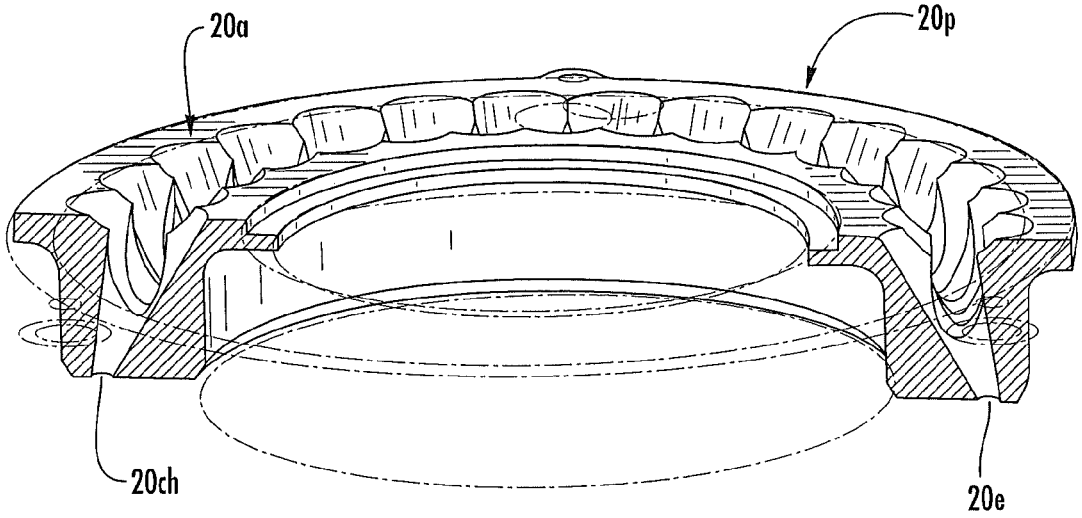


FIG. 22B

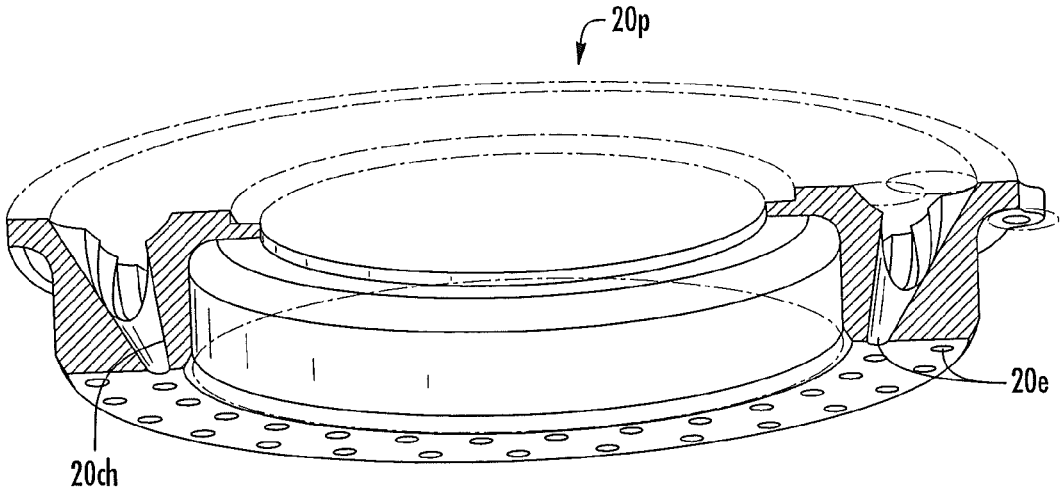


FIG. 22C

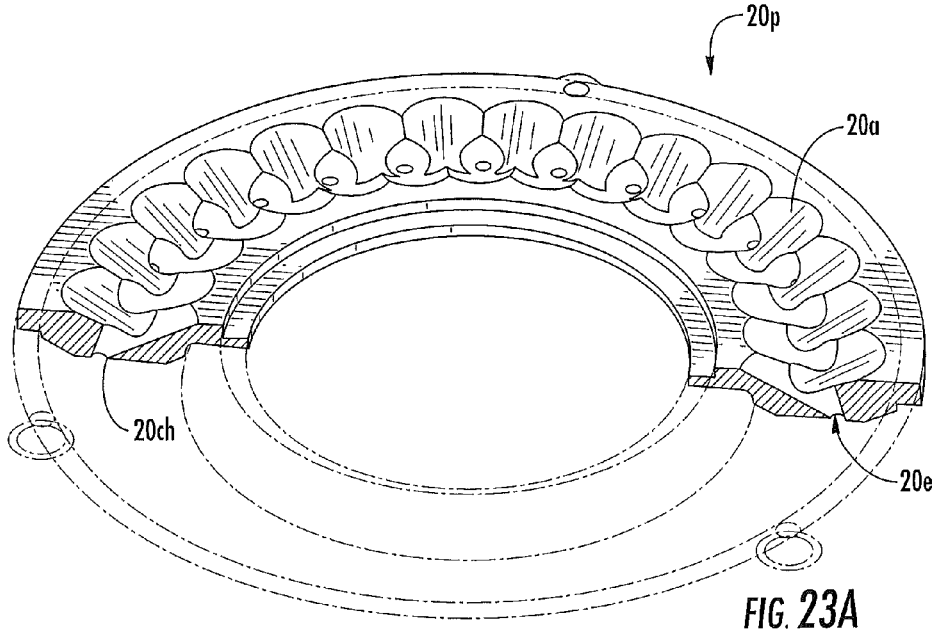


FIG. 23A

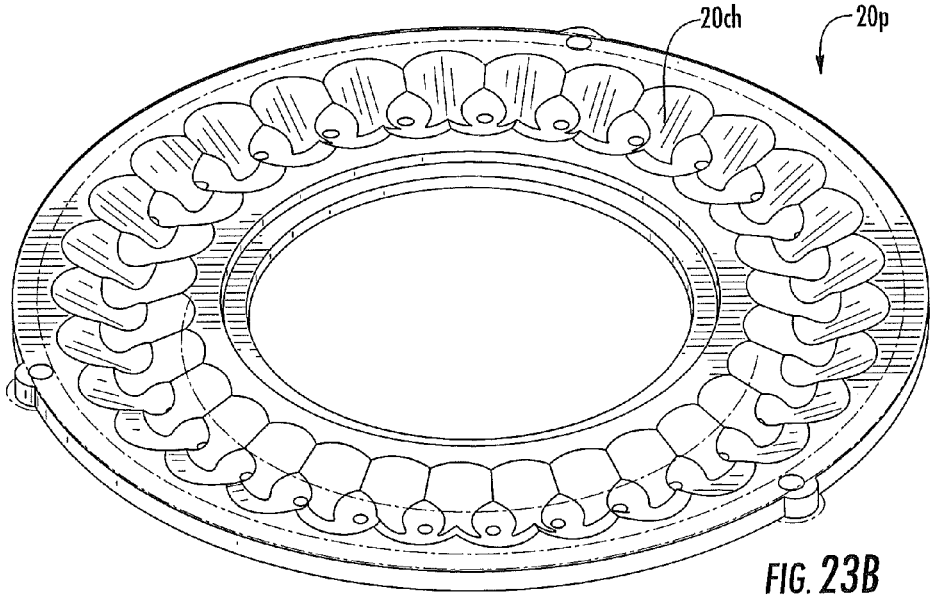


FIG. 23B

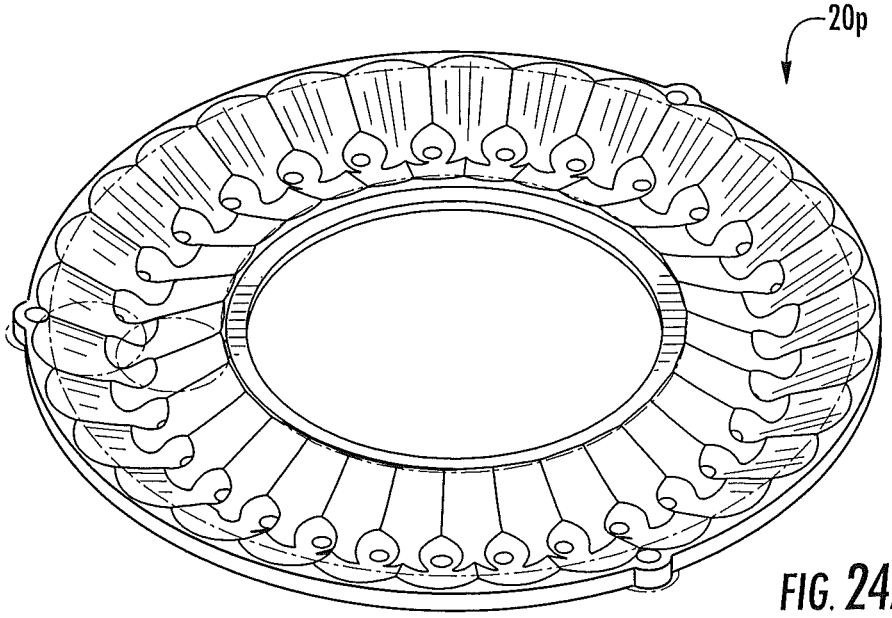


FIG. 24A

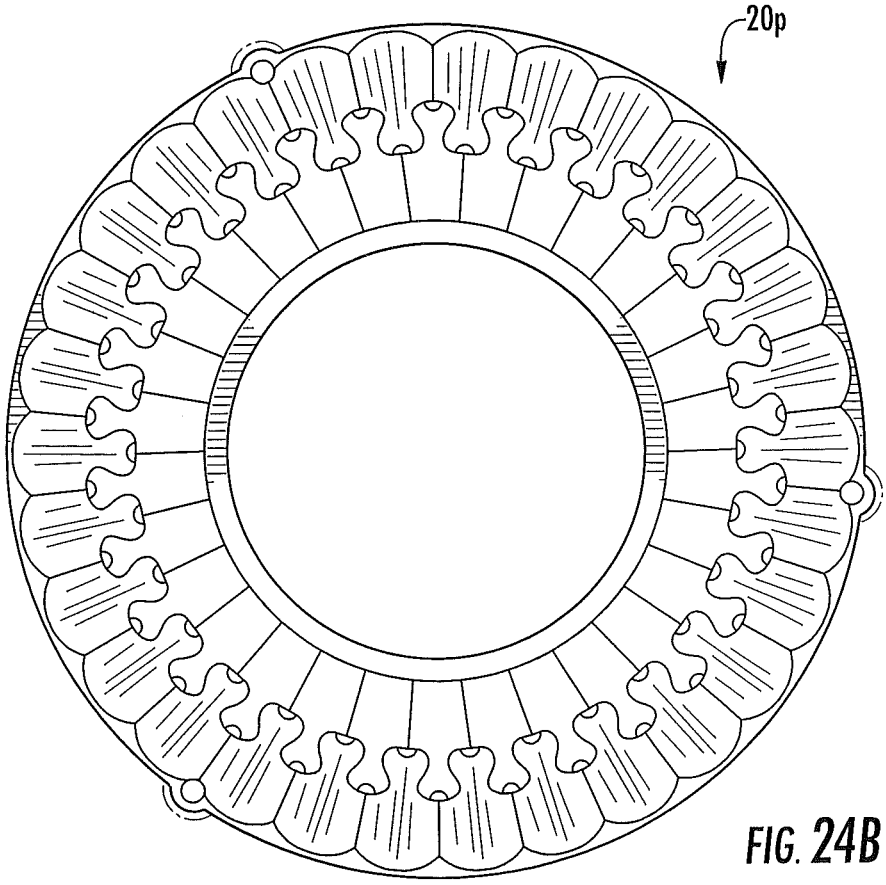


FIG. 24B

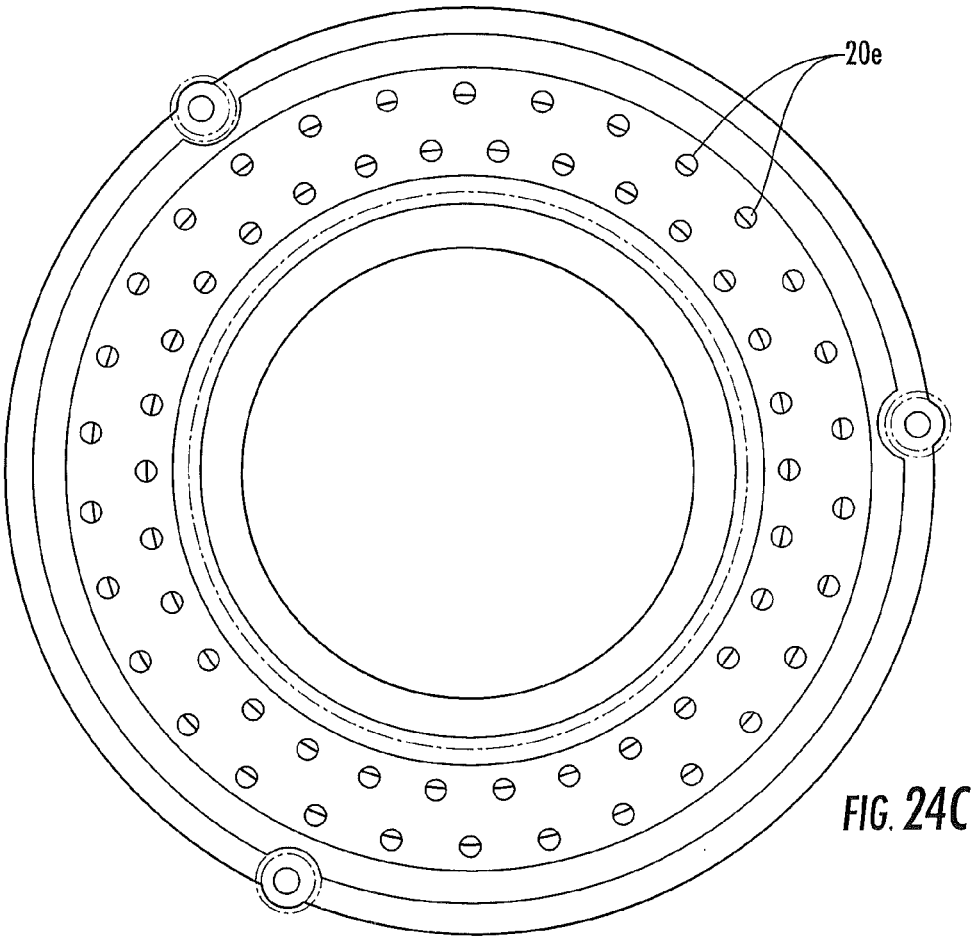


FIG. 24C

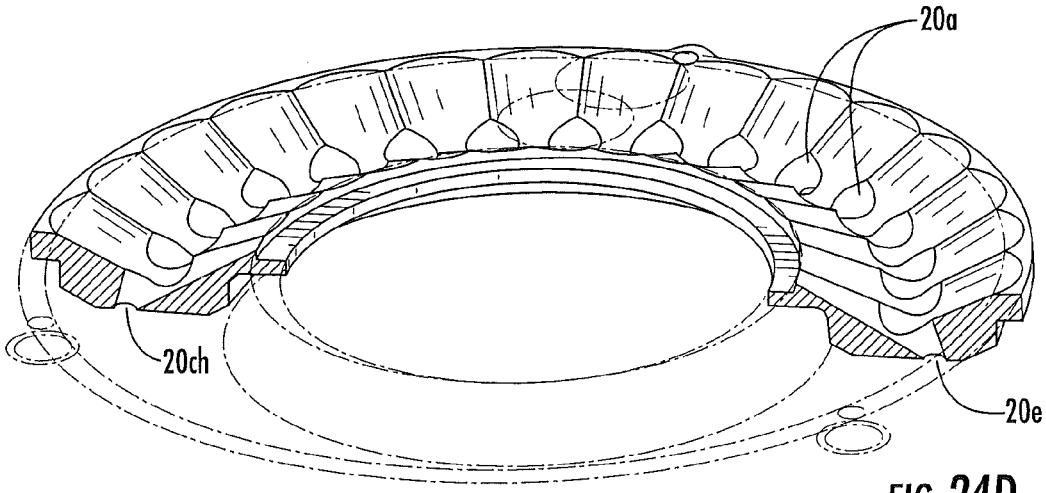


FIG. 24D

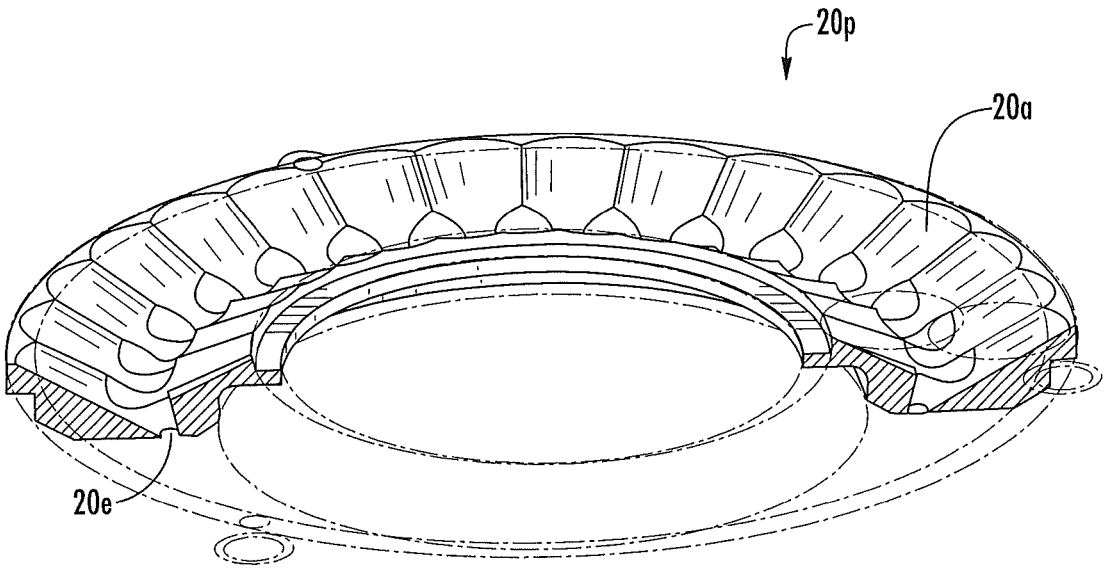


FIG. 24E

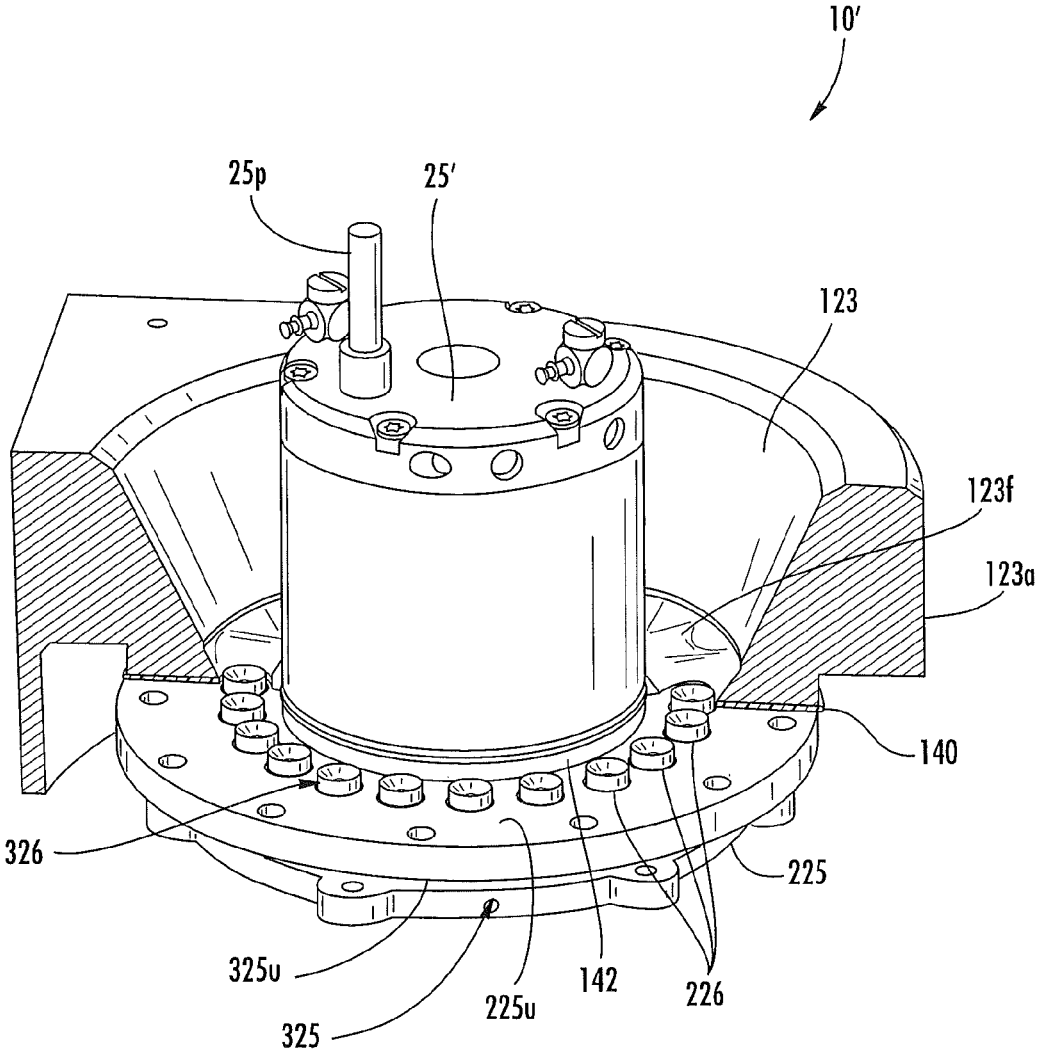


FIG. 25A

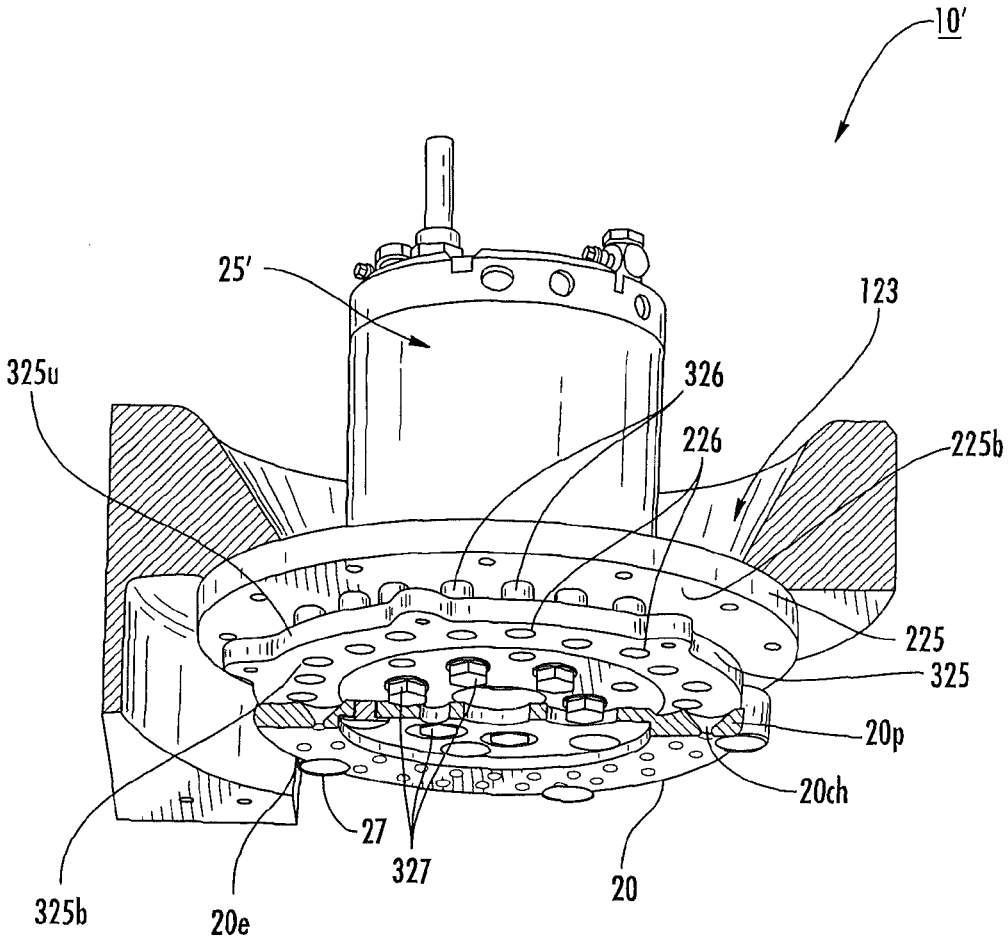


FIG. 25B

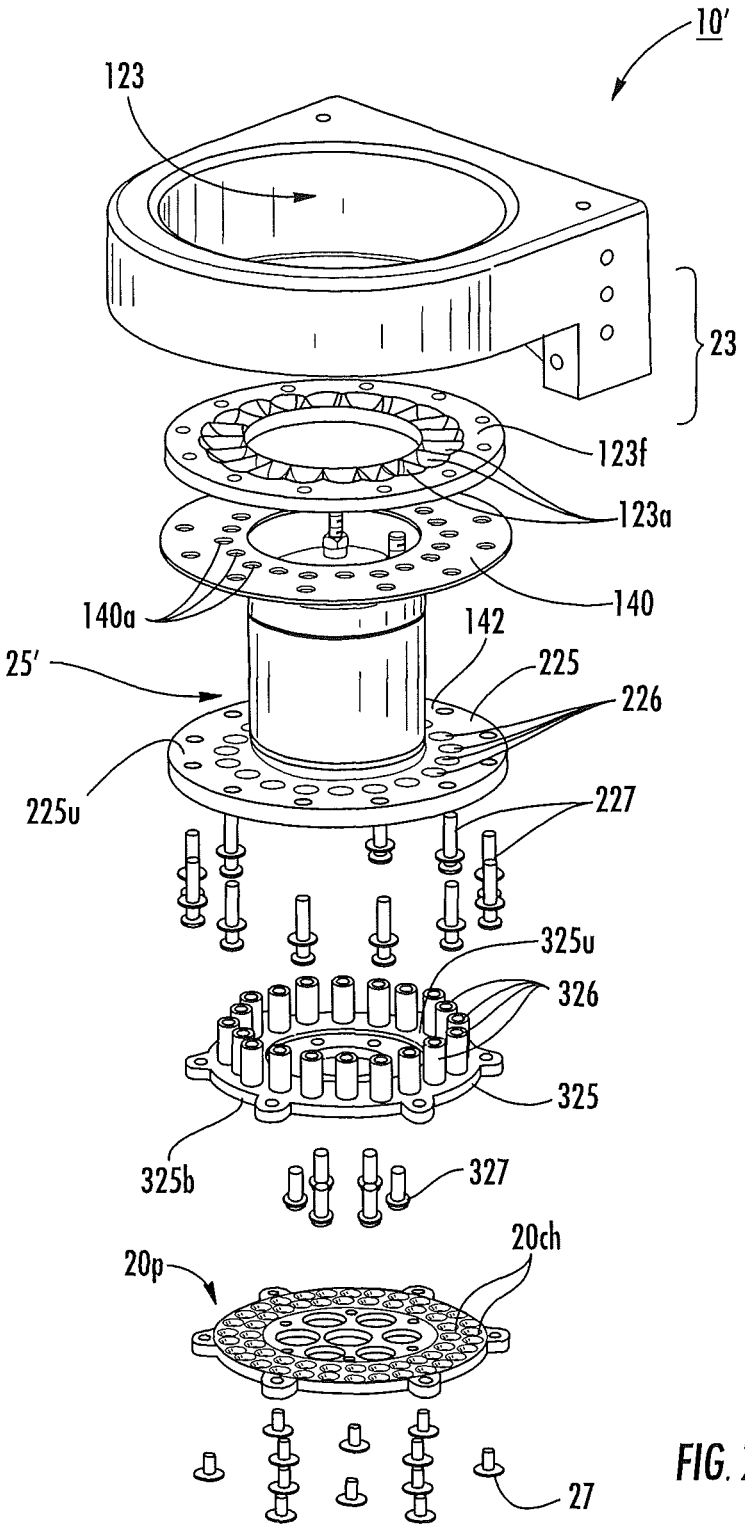

10'
123
23
123f
123a
140
140a
142
25'
225
226
225u
227
325u
326
325
325b
327
20ch
20p
27

FIG. 26

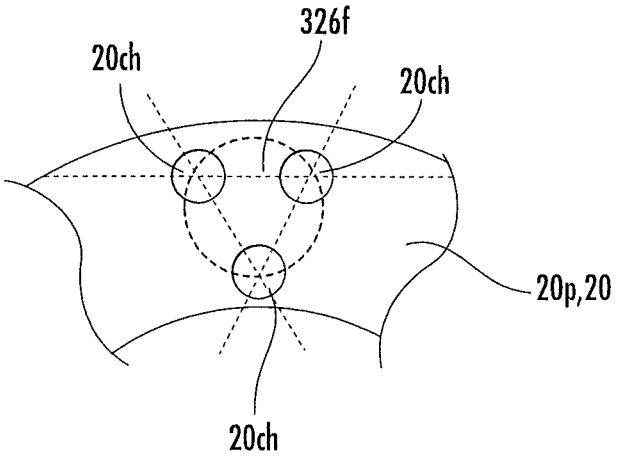


FIG. 27

DIRECT FILL DRY POWDER SYSTEMS WITH DOSING HEADS CONFIGURED FOR ON/OFF CONTROLLED FLOW

RELATED APPLICATIONS

This application is a divisional application of U.S. patent application Ser. No. 13/029,356, filed Feb. 17, 2011, which claims the benefit of and priority to U.S. Provisional Patent Application Ser. No. 61/306,291, filed Feb. 19, 2010, the contents of which are hereby incorporated by reference as if recited in full herein.

FIELD OF THE INVENTION

The present invention relates to systems for filling containers with dry powder such as drugs, chemicals and toners and may be particularly suitable for filling multi-dose disks or other containers for dry powder inhalers.

BACKGROUND OF THE INVENTION

Known dry powder dose filling devices use injectors, pistons or sleeves, such as described in U.S. Pat. Nos. 3,847,191, 4,116,247, 4,850,259, and 6,886,612. Despite the above, there remains a need for alternate dose filling systems.

SUMMARY OF EMBODIMENTS OF THE INVENTION

Embodiments of the invention provide dosing heads with a plurality of spaced apart elongate channels that communicate with a dry powder bed to concurrently directly fill a plurality of aligned dose containers.

Embodiments of the invention provide a relatively high-speed filling process for concurrently filling all the dose containers held by a dose container member, such as a disk, in sub-second time.

In some embodiments, the dosing head has at least one row of circumferentially spaced apart elongate channels (e.g., 30) and can directly fill an underlying dose container disk with an aligned row of spaced apart concentric dose containers (typically in less than about 1 second). In particular embodiments, the dosing head has two radially spaced apart circular rows of elongate channels, e.g., two rows of 30 channels arranged in a circle.

The dosing head can include at least one plate that provides the elongate channels. The dosing head can be configured to interchangeably hold different plates with different elongate channel geometries for accommodating specific dose container form factors and/or for use with different dry powder formulations. The dosing head plate can be substantially circular.

The dosing systems can be configured to fill a dose container disk with 30, 60 or, in particular embodiments, even 120 dose containers in less than about 1 second.

Some embodiments are directed to an apparatus for dispensing a defined amount of dry powder concurrently to a plurality of spaced apart dose receiving containers. The apparatus includes: (a) a dosing head comprising a support body with a plurality of spaced apart elongate channels having a channel length with an upper end defining an entry orifice and a lower end defining an exit port; (b) a dry powder bed residing above and in communication with the dosing head; and (c) at least one vibration source in communication with the dosing head channels configured to controllably apply a vibration flow signal. The channels are sized and configured to prevent a free-flow of dry powder therefrom. When the vibration flow signal is applied to the dosing head channels, dry powder from the dry powder bed flows through the elongate channels and out of the exit port. When the vibration flow signal is removed, dry powder does not flow through the dosing head elongate channels.

The spaced apart channels can be arranged so that the respective entry orifices are substantially circumferentially spaced apart in at least one circle. In some particular embodiments, the channel entry orifices are arranged in two substantially concentric circles.

The vibration source can include a substantially cylindrical body actuator mechanism with a radially extending flange having an array of circumferentially extending apertures extending therethrough. The apparatus can further include a tube plate with an array of upwardly extending tubes having upper and lower ends. The tube plate can be positioned between the actuator body flange and the dose head body so that each tube extends through a respective flange aperture with upper ends of the tubes in communication with dry powder in a dry powder hopper and lower ends of the tubes residing proximate the dosing head channels.

The channels can have orifices that have a diameter of about 3 mm or less and a geometry that defines a miniature-hopper selected to provide an on/off flow pattern and mass flow rate to deliver a defined dose amount in the range of between about 0.5-15 mg.

The channels can be sloped along at least a major portion of the channel length. For example, the channels can slope downward at an angle that is between about 30 degrees to about 45 degrees for at least a major portion of the length of the channel. The channels may have a first portion that angles downwardly to merge into a second portion that is substantially vertical at the exit port.

In some embodiments, the dosing head includes a holder with upstanding sidewalls and a lower inwardly extending ledge. The dosing head can include a plate that mounts to the holder and resides on the ledge and the plate defines the channels.

In some embodiments, the dosing head includes at least one substantially circular plate that defines the channels, the plate having a center. The apparatus can include an upstanding rod that is aligned with the center of the plate. The rod is in communication with the plate and the vibration source to apply the vibration flow signal to the plate.

In some embodiments, the apparatus includes a substantially circular tube plate with an array of circumferentially spaced apart tubes. The dosing head body can be defined by a substantially circular orifice plate that includes at least one row of circumferentially spaced apart elongate channels. The vibration source can include an actuator mechanism with a substantially cylindrical body with a vertically extending centerline aligned with a vertical linear vibration axis of the orifice plate. The actuator mechanism can have a radially extending flange that is attached to the orifice plate and the tube plate. The actuator mechanism can include a plurality of linear actuators that cause the tubes to vibrate in a vertical direction to feed dry powder to the orifice plate and to apply the vibration signal to the orifice plate.

The dosing head can have a lower primary surface that is horizontally oriented. The vibration source can be substantially in-line with a vertical axis associated with the dosing head and is configured to apply energy so that the dosing head operates with a vertical displacement that is less than about 100 microns, and wherein the target dose container is a disk that is closely spaced apart from a lowermost surface of the dosing head.

The vibration source can include: (a) a plurality of actuators, one residing proximate each channel to individually apply the flow signal; (b) a single actuator that is configured to apply the flow signal to all the flow channels; or (c) a plurality of actuators, at least one for sub-groupings of the channels.

The dry powder bed can hold a dry powder having a pharmaceutically active agent including, but not limited to, bronchodilators and the bronchodilator may be used in the form of salts, esters or solvates to thereby optimize the activity and/or stability of the medicament.

The dosing head can include at least one plate that defines at least some of the channels, and wherein the dosing head is configured to releasably engage different plates having different channel geometries to thereby allow a user to dispense different dry powders.

The apparatus channels communicate with the dry powder bed to define miniature hoppers that each hold a plurality of bolus amounts of dry powder and controllably directly dispense a bolus amount to an aligned dose container in response to the on and off application of the vibration flow signal.

Other embodiments are directed to methods of filling a dose container disk assembly. The methods include: (a) providing a dose container disk having upper and lower primary surfaces with a plurality of circumferentially spaced apart apertures associated with dose containers; (b) placing the dose container disk under a dosing head that resides below a dry powder bed, the dosing head having a plurality of circumferentially spaced apart dose filling channels with respective exit ports over the dose container disk so that the exit ports are aligned with the dose disk apertures; (c) applying a vibration flow signal to the dosing head to cause the dry powder to concurrently flow out of the channels into the dose disk apertures; (d) directly filling the dose container disk with a defined amount of dry powder in response to the applying step; and (e) ceasing the applying step to stop the flow of dry powder thereby filling a dose container disk with a defined amount of dry powder in each of the dose containers.

The flow vibration signal can be in-line and can be a frequency modified (modulated) signal. The dose container disk can have at least 30 apertures and the dosing head has at least 30 dose filling channels, and the filling step is carried out to fill at least 30 dose containers on a disk or other substrate in less than 1 second, typically in less than 0.5 seconds.

The dosing head can be attached to a tube plate that includes an array of upwardly extending tubes that communicate with the dry powder bed. The applying step can be carried out to also cause the tubes to vibrate up and down to feed the dosing head channels (which may optionally reside in a lower orifice plate).

Yet other embodiments are directed to dosing heads for a powder filling system that include a plurality of circumferentially spaced apart filling channels with exit ports residing on inner and outer radially spaced apart rows.

The dosing head can include a circular orifice plate that holds the filling channels.

The dosing head can be in combination with a tube plate attached to the orifice plate and an actuator mechanism with a radially extending flange with an array of apertures attached to the tube plate and the orifice plate.

The tube plate can have upper and lower planar surfaces with the upper surface having at least one row of upwardly extending circumferentially spaced apart tubes positioned so that the upwardly extending tubes of the tube plate extend through the flange apertures and the tube plate resides between the orifice plate and the actuator flange.

It is noted that aspects of the invention described with respect to one embodiment, may be incorporated in a different embodiment although not specifically described relative thereto. That is, all embodiments and/or features of any embodiment can be combined in any way and/or combination. Applicant reserves the right to change any originally filed claim or file any new claim accordingly, including the right to be able to amend any originally filed claim to depend from and/or incorporate any feature of any other claim although not originally claimed in that manner. These and other objects and/or aspects of the present invention are explained in detail in the specification set forth below.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a side perspective view of a filling system according to embodiments of the present invention.

FIGS. **2**A and **2**B are schematic cross-sectional views of a dose filling head and aligned dose containers for filling according to embodiments of the present invention.

FIG. **3**A is a top perspective view of a dose container disk according to some embodiments of the present invention.

FIG. **3**B is a top perspective view of a dose container disk according to some other embodiments of the present invention.

FIG. **3**C is a partial section view of an exemplary disk container configuration for dose containers associated with the dose container disk of FIG. **3**A or **3**B according to embodiments of the present invention.

FIG. **3**D is a partial section view of another exemplary dose container configuration for dose containers associated with the dose container disk of FIG. **3**A or **3**B according to embodiments of the present invention.

FIG. **4** is a sectional view taken along line **4**-**4** of FIG. **1**.

FIG. **5**A is a perspective view of a filling system according to embodiments of the present invention.

FIG. **5**B is a partial cutaway view of the filling system shown in FIG. **5**A.

FIG. **5**C is a partial cutaway side perspective view the dosing head shown in FIG. **5**A according to embodiments of the present invention.

FIG. **5**D is a side partial sectional view of the dosing head shown in FIG. **5**C.

FIG. **5**E is a perspective partial cutaway view of the dosing head shown in FIG. **5**C.

FIG. **6** is an enlarged side perspective view of a plate with dosing channels according to embodiments of the present invention.

FIG. **7** is an enlarged side perspective view of another example of a plate with dosing channels according to embodiments of the present invention.

FIG. **8**A is a side sectional view of the plate shown in FIG. **7** according to some embodiments of the present invention.

FIG. **8**B is a side sectional view of the plate shown in FIG. **6** according to some embodiments of the present invention.

FIG. **8**C is an alternate side sectional view of the plate shown in FIG. **7** according to yet other embodiments of the present invention.

FIG. **9**A is a schematic fragmented sectional view of a dosing channel with a sloping geometry and aligned dose container member according to embodiments of the present invention.

FIG. **9**B is a schematic fragmented sectional view of a dosing channel with an alternate sloping geometry and aligned dose container member according to embodiments of the present invention.

FIG. **10** is a schematic sectional view of different exemplary channel geometries according to embodiments of the present invention.

FIG. **11** is a schematic illustration of a filling system with interchangeable dosing heads or portions thereof (e.g., plates) with different channel geometries according to embodiments of the present invention.

FIGS. **12**A and **12**B are schematic illustrations of exemplary dose filling systems with multiple filling stations according to embodiments of the present invention.

FIG. **12**C is an enlarged section view of an exemplary holder for aligning a dose container member with a dosing head and/or dosing channels according to embodiments of the present invention.

FIG. **13** is a control circuit diagram of a filling system according to embodiments of the present invention.

FIG. **14** is a flow chart of operations that can be used to fill at least one dose container member with multiple dose containers according to some embodiments of the present invention.

FIG. **15** is a schematic illustration of a data processing system according to embodiments of the present invention.

FIG. **16** is a graph showing data for flow channels with different geometries and "no flow", "flow with vibration" and "free flow" limits with respect to channel outer diameter sizes (mm) and minimum displacement.

FIG. **17**A is a top perspective view of a plate with about 41 degree funnel shaped channels.

FIG. **17**B is a top perspective view of a plate with about 30 degree funnel shaped channels.

FIG. **17**C is a top perspective view of a plate with substantially cylindrical (vertical) channels.

FIG. **17**D is a graph of flow of Inh230 dry powder with "hand tapping", "no flow" and "free flow" with respect to channel size (OD) for different geometry dosing flow channels.

FIG. **18** is a graph of flow (mg/second) versus displacement (microns) for a 0.9 mm, 41 degree inverted funnel channel geometry.

FIG. **19** is graph illustrating a minimum threshold displacement (microns/micrometers) to induce flow (at 300 Hz for Inh230) versus channel nominal outer diameter size (mm) for three different channel geometries, cylindrical, 30 and 41 degree funnels.

FIG. **20**A is a graph of flow (mg/s) versus channel OD (nominal OD in mm at minimum displacement for flow using a 300 Hz vibratory signal for Inh230.

FIG. **20**B is a graph of flow rate (mg/s) versus channel area (mm^2) for a 41 degree funnel.

FIG. **21**A is a top perspective cutaway view of a dosing head with alternating inward and outward sloping channels according to embodiments of the present invention.

FIG. **21**B is a bottom perspective cutaway view of the device shown in FIG. **21**A.

FIG. **21**C is a top view of the device shown in FIG. **21**A.

FIG. **21**D is a bottom view of the device shown in FIG. **21**A.

FIG. **22**A is a top view of another embodiment of a dosing head with alternating inward and outward sloping channels according to embodiments of the present invention.

FIG. **22**B is a side perspective cutaway view of the device shown in FIG. **22**A.

FIG. **22**C is a bottom perspective view of the device shown in FIG. **22**A.

FIG. **23**A is a cutaway view of yet another embodiment of a dosing head with alternating inward and outward sloping channels according to embodiments of the present invention.

FIG. **23**B is a top perspective view of the device shown in FIG. **23**A.

FIG. **24**A is a top perspective view of a dosing head with alternating inward and outward sloping channels similar to that shown in FIG. **23**A but with larger exit ports according to embodiments of the present invention.

FIG. **24**B is a top view of the device shown in FIG. **24**A.

FIG. **24**C is a bottom view of the device shown in FIG. **24**A.

FIG. **24**D is a cutaway view of the device shown in FIG. **24**A.

FIG. **24**E is another cutaway view of the device shown in FIG. **24**A.

FIG. **25**A is a partial cutaway top view of a dose filling system according to embodiments of the present invention.

FIG. **25**B is a partial cutaway bottom view of the dose filling system shown in FIG. **25**A.

FIG. **26** is an exploded view of the system shown in FIG. **25**A.

FIG. **27** is a schematic illustration of an example filling tube to orifice channel alignment according to some particular embodiments of the present invention.

DESCRIPTION OF EMBODIMENTS OF THE INVENTION

The present invention will now be described more fully hereinafter with reference to the accompanying figures, in which embodiments of the invention are shown. This invention may, however, be embodied in many different forms and should not be construed as limited to the embodiments set forth herein. Like numbers refer to like elements throughout. In the figures, certain layers, components or features may be exaggerated for clarity, and broken lines illustrate optional features or operations unless specified otherwise. In addition, the sequence of operations (or steps) is not limited to the order presented in the figures and/or claims unless specifically indicated otherwise. In the drawings, the thickness of lines, layers, features, components and/or regions may be exaggerated for clarity and broken lines illustrate optional features or operations, unless specified otherwise. Features described with respect to one figure or embodiment can be associated with another embodiment of figure although not specifically described or shown as such.

It will be understood that when a feature, such as a layer, region or substrate, is referred to as being "on" another feature or element, it can be directly on the other feature or element or intervening features and/or elements may also be present. In contrast, when an element is referred to as being "directly on" another feature or element, there are no intervening elements present. It will also be understood that, when a feature or element is referred to as being "connected", "attached" or "coupled" to another feature or element, it can be directly connected, attached or coupled to the other element or intervening elements may be present. In contrast, when a feature or element is referred to as being "directly connected", "directly attached" or "directly coupled" to another element, there are no intervening elements present. Although described or shown with respect to one embodiment, the features so described or shown can apply to other embodiments.

The terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention. As used herein, the singular forms "a", "an" and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise. It will be further understood that the terms "comprises" and/or "com-

prising," when used in this specification, specify the presence of stated features, steps, operations, elements, and/or components, but do not preclude the presence or addition of one or more other features, steps, operations, elements, components, and/or groups thereof. As used herein, the term "and/or" includes any and all combinations of one or more of the associated listed items.

Spatially relative terms, such as "under", "below", "lower", "over", "upper" and the like, may be used herein for ease of description to describe one element or feature's relationship to another element(s) or feature(s) as illustrated in the figures. It will be understood that the spatially relative terms are intended to encompass different orientations of the device in use or operation in addition to the orientation depicted in the figures. For example, if a device in the figures is inverted, elements described as "under" or "beneath" other elements or features would then be oriented "over" the other elements or features. Thus, the exemplary term "under" can encompass both an orientation of over and under. The device may be otherwise oriented (rotated 90 degrees or at other orientations) and the spatially relative descriptors used herein interpreted accordingly. Similarly, the terms "upwardly", "downwardly", "vertical", "horizontal" and the like are used herein for the purpose of explanation or relative descriptor only unless specifically indicated otherwise.

It will be understood that although the terms "first" and "second" are used herein to describe various components, regions, layers and/or sections, these regions, layers and/or sections should not be limited by these terms. These terms are only used to distinguish one component, region, layer or section from another component, region, layer or section. Thus, a first component, region, layer or section discussed below could be termed a second component, region, layer or section, and vice versa, without departing from the teachings of the present invention. Like numbers refer to like elements throughout.

Unless otherwise defined, all terms (including technical and scientific terms) used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. It will be further understood that terms, such as those defined in commonly used dictionaries, should be interpreted as having a meaning that is consistent with their meaning in the context of the specification and relevant art and should not be interpreted in an idealized or overly formal sense unless expressly so defined herein. Well-known functions or constructions may not be described in detail for brevity and/or clarity.

In the description of the present invention that follows, certain terms are employed to refer to the positional relationship of certain structures relative to other structures. As used herein, the term "front" or "forward" and derivatives thereof refer to the general or primary direction that the dry powder travels from a powder bed to a receiving container such as a dose disk; this term is intended to be synonymous with the term "downstream," which is often used in manufacturing or material flow environments to indicate that certain material traveling or being acted upon is farther along in that process than other material. Conversely, the terms "rearward" and "upstream" and derivatives thereof refer to the direction opposite, respectively, the forward or downstream direction.

The term "deagglomeration" and its derivatives refer to flowing or processing dry powder to inhibit the dry powder from remaining or becoming agglomerated or cohesive.

The term "free-flow" refers to the ability of a channel to allow dry powder to flow therethrough when in an operative position and in the absence of any vibratory flow signal.

The filling systems can be particularly suitable for filling a partial or bolus dose or doses of one or more types of particulate dry powder substances that are formulated for in vivo inhalant dispersion (using an inhaler) to subjects, including, but not limited to, animal and, typically, human subjects. The inhalers can be used for nasal and/or oral (mouth) respiratory inhalation delivery, but are typically oral inhalers.

The terms "sealant", "sealant layer" and/or "sealant material" includes configurations that have at least one layer of at least one material and can be provided as a continuous layer that covers the entire upper surface and/or lower surface or may be provided as strips or pieces to cover portions of the device, e.g., to reside over at least one or more of the dose container apertures. Thus, terms "sealant" and "sealant layer" include single and multiple layer materials, typically comprising at least one foil layer. The sealant or sealant layer can be a thin multi-layer laminated sealant material with elastomeric and foil materials. The sealant layer can be selected to provide drug stability as they may contact the dry powder in the respective dose containers.

The sealed dose containers can be configured to inhibit oxygen and moisture penetration to provide a sufficient shelf life.

The term "primary surface" refers to a surface that has a greater area than another surface and the primary surface can be substantially planar or may be otherwise configured. For example, a primary surface can include protrusions or recesses, such as where some blister configurations are used. Thus, a component such as a disk and/or plate can have upper and lower primary surfaces and a minor surface (e.g., a wall with a thickness) that extends between and connects the two.

The dry powder substance may include one or more active pharmaceutical constituents as well as biocompatible additives that form the desired formulation or blend. As used herein, the term "dry powder" is used interchangeably with "dry powder formulation" and means that the dry powder can comprise one or a plurality of constituents, agents or ingredients with one or a plurality of (average) particulate size ranges. The term "low-density" dry powder means dry powders having a density of about 0.8 g/cm^3 or less. In particular embodiments, the low-density powder may have a density of about 0.5 g/cm^3 or less. The dry powder may be a dry powder with cohesive or agglomeration tendencies.

The term "filling" means providing a bolus or sub-bolus metered or defined amount of dry powder. Thus, the respective dose container is not required to be volumetrically full.

The term "direct" with respect to filling means that no additional components are required to carry out the operation, e.g., the dry powder is directly deposited from the dosing head channel into a blister or other dose container.

As will be appreciated by one of skill in the art, embodiments or aspects of the invention may be embodied as a method, system, data processing system, or computer program product. Accordingly, the present invention may take the form of an entirely software embodiment or an embodiment combining software and hardware aspects, all generally referred to herein as a "circuit" or "module."

In any event, individual dispensable quantities of dry powder formulations can comprise a single ingredient or a plurality of ingredients, whether active or inactive. The inactive ingredients can include additives added to enhance flowability or to facilitate aerosolization delivery to the desired target. The dry powder drug formulations can include active particulate sizes that vary. The systems may be particularly suitable for filling dry powder formulations having particulates which are in the range of between about 0.5-50 μm, typically in the range of between about 0.5 μm-20.0 μm, and more typically

in the range of between about 0.5 μm-8.0 μm. The dry powder formulation can also include flow-enhancing ingredients, which typically have particulate sizes that may be larger than the active ingredient particulate sizes. In certain embodiments, the flow-enhancing ingredients can include excipients having particulate sizes on the order of about 50-100 μm. Examples of excipients include lactose and trehalose. Other types of excipients can also be employed, such as, but not limited to, sugars which are approved by the United States Food and Drug Administration ("FDA") as cryoprotectants (e.g., mannitol) or as solubility enhancers (e.g., cyclodextrine) or other generally recognized as safe ("GRAS") excipients.

"Active agent" or "active ingredient" as described herein includes an ingredient, agent, drug, compound, or composition of matter or mixture, which provides some pharmacologic, often beneficial, effect. This includes foods, food supplements, nutrients, drugs, vaccines, vitamins, and other beneficial agents. As used herein, the terms further include any physiologically or pharmacologically active substance that produces a localized and/or systemic effect in a patient.

The active ingredient or agent that can be delivered includes antibiotics, antiviral agents, anepileptics, analgesics, anti-inflammatory agents and bronchodilators, and may be inorganic and/or organic compounds, including, without limitation, drugs which act on the peripheral nerves, adrenergic receptors, cholinergic receptors, the skeletal muscles, the cardiovascular system, smooth muscles, the blood circulatory system, synoptic sites, neuroeffector junctional sites, endocrine and hormone systems, the immunological system, the reproductive system, the skeletal system, autacoid systems, the alimentary and excretory systems, the histamine system, and the central nervous system. Suitable agents may be selected from, for example and without limitation, polysaccharides, steroids, hypnotics and sedatives, psychic energizers, tranquilizers, anticonvulsants, muscle relaxants, anti-Parkinson agents, analgesics, anti-inflammatories, muscle contractants, antimicrobials, antimalarials, hormonal agents including contraceptives, sympathomimetics, polypeptides and/or proteins (capable of eliciting physiological effects), diuretics, lipid regulating agents, antiandrogenic agents, antiparasitics, neoplastics, antineoplastics, hypoglycemics, nutritional agents and supplements, growth supplements, fats, antienteritis agents, electrolytes, vaccines and diagnostic agents.

The active agents may be naturally occurring molecules or they may be recombinantly produced, or they may be analogs of the naturally occurring or recombinantly produced active agents with one or more amino acids added or deleted. Further, the active agent may comprise live attenuated or killed viruses suitable for use as vaccines. Where the active agent is insulin, the term "insulin" includes natural extracted human insulin, recombinantly produced human insulin, insulin extracted from bovine and/or porcine and/or other sources, recombinantly produced porcine, bovine or other suitable donor/extraction insulin and mixtures of any of the above. The insulin may be neat (that is, in its substantially purified form), but may also include excipients as commercially formulated. Also included in the term "insulin" are insulin analogs where one or more of the amino acids of the naturally occurring or recombinantly produced insulin has been deleted or added.

It is to be understood that more than one active ingredient or agent may be incorporated into the aerosolized active agent formulation and that the use of the term "agent" or "ingredient" in no way excludes the use of two or more such agents. Indeed, some embodiments of the present invention contemplate filling a single dose container or a single disk with combination drugs that may be mixed in situ.

Examples of diseases, conditions or disorders that may be treated using dry powder filled with the filling systems of embodiments of the invention include, but are not limited to, asthma, COPD (chronic obstructive pulmonary disease), viral or bacterial infections, influenza, allergies, cystic fibrosis, and other respiratory ailments as well as diabetes and other insulin resistance disorders. The dry powder may be used to deliver locally-acting agents such as antimicrobials, protease inhibitors, and nucleic acids/oligionucleotides as well as systemic agents such as peptides like leuprolide and proteins such as insulin. For example, inhaler-based delivery of antimicrobial agents such as antitubercular compounds, proteins such as insulin for diabetes therapy or other insulin-resistance related disorders, peptides such as leuprolide acetate for treatment of prostate cancer and/or endometriosis and nucleic acids or ogligonucleotides for cystic fibrosis gene therapy may be performed. See e.g. Wolff et al., *Generation of Aerosolized Drugs*, J. Aerosol. Med. pp. 89-106 (1994). See also U.S. Patent Application Publication No. 20010053761, entitled *Method for Administering ASPB28-Human Insulin* and U.S. Patent Application Publication No. 20010007853, entitled *Method for Administering Monomeric Insulin Analogs*, the contents of which are hereby incorporated by reference as if recited in full herein.

Typical dose amounts of the unitized dry powder mixture dispersed by inhalers may vary depending on the patient size, the systemic target, and the particular drug(s). The dose amounts and type of drug held by a dose container (also known as a "dose container system") may vary per dose container or may be the same on a platform such as a disk. In some embodiments, the dry powder dose amounts can be about 100 mg or less, typically less than 50 mg, and more typically between about 0.1 mg to about 30 mg.

In some embodiments, such as for pulmonary conditions (i.e., asthma or COPD), the dry powder can be provided as about 5 mg total weight (the dose amount may be blended to provide this weight). A conventional exemplary dry powder dose amount for an average adult is less than about 50 mg, typically between about 10-30 mg and for an average adolescent pediatric subject is typically from about 5-10 mg. A typical dose concentration may be between about 1-5%. Exemplary dry powder drugs include, but are not limited to, albuterol, fluticasone, beclamethasone, cromolyn, terbutaline, fenoterol, β-agonists (including long-acting β-agonists), salmeterol, formoterol, cortico-steroids and glucocorticoids.

In certain embodiments, the bolus or dose can be formulated with an increase in concentration (an increased percentage of active constituents) over conventional blends. Further, the dry powder formulations may be configured as a smaller administrable dose compared to the conventional 10-25 mg doses. For example, each administrable dry powder dose may be on the order of less than about 60-70% of that of conventional doses. In certain particular embodiments, using the dispersal systems provided by certain embodiments of the DPI configurations of the instant invention, the adult dose may be reduced to under about 15 mg, such as between about 10 μg-10 mg, and more typically between about 50 μg-10 mg. The active constituent(s) concentration may be between about 5-10%. In other embodiments, active constituent concentrations can be in the range of between about 10-20%, 20-25%, or even larger. In particular embodiments, such as for nasal inhalation, target dose amounts may be between about 12-100 μg.

In certain particular embodiments, the dry powder in the filling system for a particular dose container, drug compart-

ment or blister may be formulated in high concentrations of an active pharmaceutical constituent(s) substantially without additives (such as excipients). As used herein, "substantially without additives" means that the dry powder is in a substantially pure active formulation with only minimal amounts of other non-biopharmacological active ingredients. The term "minimal amounts" means that the non-active ingredients may be present, but are present in greatly reduced amounts, relative to the active ingredient(s), such that they comprise less than about 10%, and preferably less than about 5%, of the dispensed dry powder formulation, and, in certain embodiments, the non-active ingredients are present in only trace amounts.

In some embodiments, the target unit dose amount of dry powder for a respective drug compartment or dose container is between about 5-15 mg, typically less than about 10 mg, such as about 5 mg of blended drug and lactose or other additive (e.g., 5 mg LAC), for treating pulmonary conditions such as asthma. Insulin may be provided in quantities of about 4 mg or less, typically about 3.6 mg of pure insulin. The dry powder may be inserted into a dose container/drug compartment in a "compressed" or partially compressed manner or may be provided as free flowing particulates.

The filling can be carried out to fill dose containers in any suitable number of doses, typically between about 30-120 doses, and more typically between about 30-60 doses.

Certain embodiments may be particularly suitable for dispensing medication to respiratory patients, diabetic patients, cystic fibrosis patients, or for treating pain. The inhalers may also be used to dispense narcotics, hormones and/or infertility treatments.

The dose filling systems may be particularly suitable for dispensing medicament for the treatment of respiratory disorders. Appropriate medicaments may be selected from, for example, analgesics, e.g., codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, e.g., diltiazem; antiallergics, e.g., cromoglycate, ketotifen or nedocromil; antiinfectives e.g., cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, e.g., methapyrilene; anti-inflammatories, e.g., beclomethasone dipropionate, fluticasone propionate, flunisolide, budesonide, rofleponide, mometasone furoate or triamcinolone acetonide; antitussives, e.g., noscapine; bronchodilators, e.g., albuterol, salmeterol, ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, terbutaline, isoetharine, tulobuterol, or (−)-4-amino-3,5-dichloro-α-[[6-[2-(2-pyridinyl)ethoxy] hexyl]methyl]benzenemethanol; diuretics, e.g., amiloride; anticholinergics, e.g., ipratropium, tiotropium, atropine or oxitropium; hormones, e.g., cortisone, hydrocortisone or prednisolone; xanthines, e.g., aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; therapeutic proteins and peptides, e.g., insulin or glucagon. It will be clear to a person of skill in the art that, where appropriate, the medicaments may be used in the form of salts, (e.g., as alkali metal or amine salts or as acid addition salts) or as esters (e.g., lower alkyl esters) or as solvates (e.g., hydrates) to optimize the activity and/or stability of the medicament.

Some particular embodiments of the filling system can be used to dispense meted quantities of medicaments that are selected from the group consisting of: albuterol, salmeterol, fluticasone propionate and beclometasone dipropionate and salts or solvates thereof, e.g., the sulphate of albuterol and the xinafoate of salmeterol. Medicaments can also be delivered in combinations. Examples of particular formulations containing combinations of active ingredients include those that contain salbutamol (e.g., as the free base or the sulphate salt) or salmeterol (e.g., as the xinafoate salt) in combination with an anti-inflammatory steroid such as a beclomethasone ester (e.g., the dipropionate) or a fluticasone ester (e.g., the propionate).

Turning now to the figures, FIG. **1** illustrates an example of a filling system **10**. The filling system **10** includes a dosing head **20** with a plurality of spaced apart dosing channels **20***ch*. A dry powder bed **23** with dry powder **23***p* (FIG. **2**A) resides above the channels **20***ch*. The channels **20***ch* all include inlet orifices **20***a* and opposing exit ports **20***e* and sidewalls **20***w* (FIG. **2**A). The filling system **10** includes a vibration source **25** that is in communication with the channels **20***ch*. The vibration source **25** communicates with a vibratory control circuit **28** to generate a defined vibration flow signal **28***s* which is transmitted to the dry powder channels **20***ch* for a defined time to cause dry powder **23***p* to flow out of the dosing channels **20***ch* and into aligned dose containers **30***c* to dispense a metered amount of the dry powder therein. The flow signal **28***s* can generate a small stimulation motion **28**M, typically in-line (e.g., substantially vertical) with a suitable displacement profile as will be discussed further below.

The geometry of the channel **20***ch*, including one or more of the size of the orifice **20***a*, size (volume and cross-sectional area) of the channel between entry orifice **20***a* and the exit port **20***e*, shape and length of the channel and the size and shape of the exit port can be selected so that there is no "free flow" of powder out of the exit port **20***e* when dispensing is not desired (e.g., when the vibratory flow signal is "off" or not transmitted to the flow channels).

The channel geometry and the flow signal **28***s* can be selected to define a reliable flow rate with the "on" and "off" flow control corresponding to when the flow signal is applied or withheld without requiring any physical barrier or valving of the exit ports **20***e*. The flow rates can be within a range of between about 5 mg/second to about 100 mg/second, typically between about 10 mg/second to about 30 mg/second. It may be desired to have the channel geometry and the vibration provide a sub-second filling rate, e.g., a suitable flow rate for an "on" time for the vibratory flow signal of less than about 1 second, typically about 0.5 seconds or less to fill all 30 or 60 doses (or other numbers of dose containers).

As shown in FIGS. **2**A and **2**B, during filling, the dosing head **20** can reside closely spaced apart from (but not contacting) an underlying dose container member **30** with a plurality of spaced apart dose containers **30***c*. The spacing can be at distance "d", typically between about 0.1 mm to about 2.0 mm, and may, in some particular embodiments be between about 0.5 mm to about 1.0 mm.

FIGS. **5**A and **5**B illustrate another example of a filling system **10**. As shown in FIG. **5**B, the dosing head **20** resides closely spaced to the dose container **30**. FIG. **5**B also illustrates that the channels **20***ch* are held aligned with/registered to a corresponding dose container aperture **30***a*.

The dry powder bed **23** with the dry powder **23***p* can be enclosed in a housing or open to atmosphere but is not required to be sealed in a pressurized chamber. That is, as the geometry of the channel and the vibratory flow signal directly dispense the dry powder into aligned dose containers **30***c*. The system **10** does not require either pressure or vacuum to dispense the dry powder and the dry powder bed can be environmentally protected from exposure but is not sealed in a pressure-tight manner.

Referring to FIG. **2**A, as shown, before or after active dispensing (FIG. **2**B), at least one bolus quantity of the dry powder can reside in the dose channel **20***ch*. In this way, the channels **20***ch* act as miniature hoppers of one or a few dose

quantities of the dry powder **23**. In other embodiments, the dry powder **23***p* remains in the powder bed **23** above the channels **20***ch* and the dry powder only enters and flows through the channels when the flow signal **28***s* is applied to the dosing head **20** and/or channels **20***ch*. The latter operational configuration may be particularly true for some channel geometries, such as those with very small entry orifices or those having inverted funnel shapes (where the smallest orifice of the channel is at the top of the device in contact with the powder bed), for example.

The dry powder **23***p* in the channel can be replenished via a powder bed residing directly above the channels **20***ch* (contacting the upper primary surface the dosing head **20** and the entry orifices **20***a*). The powder **23***p* in the powder bed **23** can be maintained at a desired level or may be allowed to fluctuate in levels, typically between defined upper and lower limits, such as between a 3 mm to a 150 mm bed height above the entry orifices **20***a*, typically between 3 mm and 15 mm. The powder **23***p* in the powder bed **23** can be continuously replenished or may be replenished based on a level sensor and/or after a defined number of dose container members **20** have been filled.

In particular embodiments, the channels **20***ch* can be sloped and/or angled to inhibit "rat-holing" or undesired trapping of the dry powder. Rat-holing refers to circumstances in which powder is retained against the walls of a length of the channel. Bridging and rat-holing can both be caused by a reduction in the channel width or cross sectional area. This may lead to the powder becoming compacted and forming stresses within the body of the powder. These stresses can lead to stable structures that are difficult to break up. This problem is usually amplified by high wall friction and a head of powder above the blockage. Although vibration can be used to break a bridge or to cause a rat hole to collapse, it can also have the adverse effect of compacting the powder.

To facilitate controlled flow, in some embodiments, as shown in FIG. **9**A (and FIGS. **17**A and **17**B), the channels **20***ch* can have an angle (e.g., slope) for a least a major portion of the length of the channel. The angle "α" can be defined with the slope of the wall defining the channel flow floor for the powder and/or with respect to the longitudinally extending centerline of the channel. The angle "α" can be between about 30 degrees to about 75 degrees from horizontal, and more typically is between about 30 degrees to about 45 degrees, such as about 40 or 41 degrees from horizontal.

FIGS. **21**A-**21**D show about a 40 degree funnel angle with overlapping entry ports **20***a* and alternating inward and outward sloping channels **20***ch*. FIGS. **22**A-**22**C show a 60 degree funnel angle with overlapping entry ports **20***a* and alternating inward and outward sloping channels **20***ch*. FIGS. **5**D and **5**E show a 60 degree channel with all of the channels **20***ch* angled inward (and with an oval top entry port **20***a* with the long sides of the oval circumferentially oriented about the plate **20***p*. FIGS. **23**A-**23**B and **24**A-**24**E show a 30 degree funnel (with overlapping entry ports **20***a* and alternating inward and outward sloping channels **20***ch*).

In some embodiments, the channels **20***ch* can have an offset geometry that can help prevent the undesired plugging or rat-holing of powder flow. That is, as shown in FIG. **9**B, in some embodiments, the channels **20***ch* can have sidewalls with one portion **21***u* with a longitudinally extending centerline **21***c* which angles or slopes downward at a first defined angle "α**1**" that merges into a lower portion **21***l* with sidewalls **20***w* that are oriented at a second different angle "α**2**", such as a lower channel portion with a vertically extending centerline **21***v* at the exit port **20***e*. Typically, the first angle α**1** is between about 30 degrees to about 75 degrees from horizontal, and more typically is between about 30 degrees to about 45 degrees, such as about 40 or 41 degrees from horizontal.

It is also noted that although shown as angling down in the right hand direction in several figures, the channels **20***ch* can slope the opposite way. Indeed, different channels in a dosing head or plate can be oriented to angle in the opposite directions, e.g., the channels **20***ch* associated with exit ports **20***e* on the outer row can angle down and outward while the channels associated with exit ports **20***e* on the inner row can angle down and inward (where two rows of concentric/circular channels are used) or vice versa. See, for example, FIGS. **21**A, **22**A, **23**A, and **24**A which illustrate alternating inward and outward sloping channels **20***ch* with 60 channels **20***ch*, 30 exit ports **20***e* on each of the inner and outer circular rows (and offset from each other).

The vibration signal **28***s* can be generated by any suitable vibratory source, including electrical means, mechanical means, electromagnetic means and/or electro-mechanical means. As shown, the vibration source **25** includes at least one actuator **25** in communication with the dosing head **20** and a vibration control circuit **28**. It is contemplated that more than one actuator may be used for each set of dosing channels or for each plate **20***p* (the dosing plate is shown in various figures, e.g., FIGS. **5**A, **8**A-**8**C, **17**A-**17**C).

The actuator(s) **25** can be configured to be substantially in-line with the dosing head **20** and one-directional. The actuator **25** can apply the flow signal (e.g., flow energy) in a substantially vertical (only) direction. As shown in FIGS. **1** and **5**A, the actuator **25** can be mounted to a rod **29** that is attached to a center of the dosing head **20**. The flow signal/energy **28***s* can be applied so that the displacement is substantially all vertical but typically so that there is limited physical vertical displacement during the dispensing step. The actuator **25** can be an in-line magnetostrictive actuator or any other suitable actuator or controllable vibrating member. For example, Model CU18 magnetostrictive actuator from Etrema Products, Ames, Iowa. The stimulation or vibration motion can have a defined displacement profile, such as a non-harmonic displacement profile. The stimulation/vibration flow signal **28***s* can be generated in-line with a vertical axis associated with the dosing head ("A") so as to apply the flow energy so that the dosing head with a vertical displacement that is less than about 25 microns. As noted above, the target dose container member **30** can be closely spaced apart from a lowermost surface of the dosing head **20**, such as between about 20-100 microns, during filling.

In other embodiments, a piezoelectric material (e.g., crystal or ceramic) with an opening that aligns to the entry orifice **20***a* can be attached to each dosing channel. This can provide an individual actuator for each channel (not shown).

The vibration signal **28***s* is selected to dispense dry powder at a defined flow rate (with acceptable variation, typically +/−5-10%) for a particular channel geometry. As noted above, the channel geometry can be selected so that the flow is controllable, e.g., there is no free-flow of powder out or through the channels **20***ch* without the flow signal **28***s*. In operation, a continual vibration signal or signals can be applied to the dosing head (or individually to the channels **20***ch*), and a "burst" of energy can be applied as the flow signal **28***s* for a short duration to carry out the filling process. For example, a vibratory signal can be applied to the dosing head/powder bed to help avoid powder segregation. A high frequency can be modulated "on" and "off" as impulses for providing the vibratory flow signal. In other embodiments, no "background" vibration is used and the vibration can be applied only to generate the flow signal. The vibration signal **28***s* can include, for example, a saw tooth, square or sine wave

associated with a waveform generator. The signal **28***s* can be configured to generate less than about an 80 micron vertical displacement of the head **20** and/or plate **20***p*. The frequency or frequencies of the flow signal **28***s* can be between about 100 Hz to about 5000 Hz, but other frequencies may be used. The vibration signal can be frequency modified, e.g., a frequency modulated sinusoidal signal. Powder-specific signals may be used. See, e.g., U.S. Pat. No. 6,985,798, the content of which is hereby incorporated by reference as if recited in full herein.

The dosing head **20** can have integrated dosing channels **20***ch* or the dosing channels **20***ch* can be provided in a plate **20***p* (FIGS. **6**, **7**, **21** et seq.) or other member that is attached to a portion of the dosing head. The plate **20***p* can be releasably attached to a frame or sidewalls of the dosing head **20** under the dry powder of the powder bed **23**. In other embodiments, one dosing head can hold a plurality of the plates in spaced apart arrangements (FIG. **12**B) and/or can include a plurality of integrated spaced apart circular dosing channels to allow for filling a plurality of disks with a single dosing head **20** and powder bed **23**.

In some embodiments, as shown in FIGS. **1**, **3**A-**3**D and **5**A-**5**C, for example, the dose container member **30** is a dose disk with at least one row of dose containers **30***c* that are circumferentially spaced apart. Thus, the dosing head **20** can include a corresponding arrangement of dosing channels **20***ch*. In some embodiments, such as shown in FIGS. **6** and **8**B, there is one entry orifice **20***a* and associated dosing channel **20***ch* for each dose container **30***c*. In other embodiments, such as shown in FIGS. **7**, and **8**A, for each dose container **30***c*, the dosing head **20** has a plurality of closely spaced entry orifices **20***a* and corresponding dosing channels **20***ch*. In other embodiments, as shown in FIG. **8**C, there can be a plurality of orifices **20***a* that open into a common dosing channel **20***ch* for a respective dose container **30***c*.

FIG. **3**A illustrates a dose container assembly **20** with a dose ring or disk **30** having a plurality of dose containers **30***c*. The dose containers **30***c* can have a volume (prior to filling and sealing) that is less than about 24 mm^3, typically between 5-15 mm^3. The powder bulk density can be about 1 g/cm^3 while the power nominal density when filled (for reference) can be about 0.5 g/cm^3. The maximum compression of a drug after filling and sealing in the dose container **30***c* can be less than about 5%, typically less than about 2%.

In some embodiments, the dosing channel exit ports **20***e* (e.g., orifice) can have a cross-sectional length or width (e.g., diameter) that is about 3.2 mm or less.

As shown in FIGS. **3**A and **3**B, in some embodiments, the dose ring or disk **30** can include a plurality of circumferentially spaced apart through apertures **30***a* that form a portion of the dose containers **30***c*. As shown in FIGS. **3**C and **3**D, the dose containers **30***c* can be defined by the dose container apertures **30***a* and upper and lower sealants **36**, **37** (after filling with the dry powder **23** therein). FIG. **3**A illustrates that the dose container disk **30** can include 60 dose containers **30***c* while FIG. **3**B illustrates that the dose container disk **30** can include 30 dose containers **30***c*. Greater or lesser numbers of dose containers may be used. As noted above, the dosing head **20** can include a like number of or at least the same number of dosing channels **20***ch* (or more if more than one dosing channel **20***ch* is used to fill a corresponding container **30***c* such as shown in FIG. **7**). The sealant layers **36**, **37** can have the same or different material(s) and may include foil, polymer(s) and/or elastomer(s), or other suitable material or combinations of materials, including laminates. Typically, the sealant layers **36**, **37** are thin flexible sealant layers comprising foil.

In other embodiments, the bottom of the dose container **30***c* may be provided by a closed floor of the substrate rather than a sealant layer. In yet other embodiments, the dose disk **30** can have a blister configuration which is filled by the dose head **20**.

FIGS. **3**A and **3**B also illustrate that the dose container disk **30** can include at least one indexing notch **34**, shown as a plurality of circumferentially spaced apart indexing notches **34**.

As shown in FIGS. **5**A-**5**E, the system **10** can include a mounting member **22** that has a threaded member **22***t* with a collar **22***c* that holds the stem **29** to the dosing head **20** to releasably engage the dosing head **20** and align the dose container **30** with the dosing head **20** using one or more of the notches **34**. For example, the holder **40** can include a spring-loaded, radially outwardly extending finger or tab that releasably engages one or more of the notches **34** to position the dose containers **30***c* so that they are aligned with channels **20***ch*. FIG. **12**C illustrates an alternate holder **40** configuration with a center post **44** with a channel **41** and upstanding outer indexing tabs **40***p*. Other holders and alignment means may be used.

As shown in FIGS. **3**A and **3**B, the dose containers **30***c* may be arranged so that they are circumferentially spaced apart in one or more rows. As shown in FIG. **3**A, the dose containers **30***c* are arranged in staggered concentric rows, a front row **31** at a first radius from a center of the disk and a back row **32** at a second different radius. Thus, the dosing channels **20***ch* and the corresponding dose containers **30***c* can be arranged so that centerlines of the dosing channels **20***ch* and dose containers **30***c* of the back row are circumferentially offset from the centerlines of the dosing channels and dose containers **30***c* in the front row by a distance. As shown in FIG. **3**A, the dose containers **30***c* on each respective row are spaced apart a distance "D" and the offset of the centerlines of those on the back row to those on the front row is "D/2". The dosing channels **20***ch* can have a corresponding layout or arrangement. The dose container disk **30** can be a molded polymer, copolymer or blends and derivatives thereof, or may comprise metal, or combinations thereof, or other materials that are capable of providing sufficient moisture resistance. The dosing head can comprise stainless steel or other suitable non-reactive material or materials that can be cleaned to meet regulatory cleanliness standards.

The dose container disk **30** can have an outer diameter of between about 50-100 mm, typically about 65 mm and a thickness of between about 2-5 mm, typically about 3 mm. The disk **30** can comprise a cyclic olefin (COC) copolymer. The apertures **30***a* can have a diameter of between about 2-5 mm, typically about 3 mm and the sidewalls **30***w* of the dose containers **30***c* may have an angle or draft of about 1-3 degrees per side, typically about 1.5 degrees, as shown in FIG. **3**D, to facilitate removal from a mold (where a molding process is used to form the disk **30**). The dose container **30** is configured to be able to protect the powder from moisture ingress, while providing a desired number of doses in a compact overall inhaler size. The individual dose container apertures **30***a* are spaced apart from each other to allow sufficient seal area and material thickness for moisture protection of the powder.

FIG. **4** illustrates an exemplary configuration of a dosing head **20** attached to the rod **29** and having a bracket **22** with a support **22***s* that engages a lower portion of the bed **23** in a manner that does not occlude any of the flow channels. The bracket **22** can include outwardly extending arms **22***a* that attach to an upper portion of the powder bed **23**. The channels

20*ch* can be integral to the bed **23** or may be provided in a plate, disk or other component that attaches to the dosing head.

FIGS. **5**A-**5**E illustrates the dosing head **20** with a lower plate **20***p* defining the channels **20***ch*. As shown in FIGS. **5**B and **5**C, for example, the plate can include an inwardly extending ledge or lip **22***l*. The plate **20***p* can reside on the ledge **22***l* and can be releasably attached to the head **20** and/or bed **23**.

Referring to FIG. **5**A, the filling system **10** can include a dose container holder **40** that registers the dose container apertures **30***a* to the filling channel exit ports **20***e* using the indexing notches **34** on the container **30** (FIGS. **3**A/**3**B). However, the system can use other components, geometry or indexing configurations to carry out the registration. For example, in other embodiments, the dosing head **20** can be configured to rotate to align with the dose containers **30***a* using optical or proximity sensors, lasers or other automated position controlled devices.

As shown in FIGS. **5**C-**5**E, **8**A-**8**C, and **21**-**24**, the dosing head plate **20***p* can have an open center space **20***o* that receives the support bracket or member **22** which is substantially in-line with the rod **29**. In some embodiments, the dosing head **20**, plate **20***p* and/or support frame **22** can be configured so that the vibration transferred by the rod **29** is substantially evenly distributed from the center to a location that is at least co-extensive with the outer row of dosing channels.

FIGS. **25**A, **25**B and **26** illustrate an alternate mounting of the actuator **25'** and dosing head **20** (which typically includes a dosing plate **20***p*, also referred to as an "orifice plate"). In this embodiment, the actuator **25'** is positioned closely spaced to the dosing head **20** so as to not require an overhead actuator and connecting rod to improve coupling of the vibration to the orifice plate/dosing head **20***p*/**20**. As before, although the dosing head **20** is shown comprising a (releasable) dosing plate **20***p*, the dosing head may be an integral body device with the channels **20***ch*. Where an orifice plate **20***p* is used, the plate **20***p* can be provided in two or more matable pieces (not shown) and may include inner or outer sidewalls that form part or all of the powder bed (also not shown). In this embodiment, the (lowermost) orifice plate **20***p* is mounted to a tube plate **325** with an array of tubes **326** that penetrate through aligned apertures **123***a* in the floor **123***f* of a (small) powder bed **23**. The combined orifice plate **20***p* and tube plate **325** can attach directly to an integrated central actuator **25'** that vibrates them. The vibrating tubes **326** help flow powder to the orifice plate **20***p* while the orifices **20***ch* still provide on/off flow control for controlled dispensing.

FIGS. **25**A, **25**B and **26** illustrate that the dry powder bed **23** can be provided by a rigid powder hopper **123** having a rigid bottom floor **123***f*. The floor **123***f* can include apertures **123***a* (FIG. **26**) that receive the array of upwardly extending tubes **326**. The floor apertures **123***a* can have geometries that funnel powder downward.

The actuator **25'** can include a radially extending planar flange **225** with a plurality of circumferentially spaced apart apertures **226**. The vibrating tubes **326** extend through these apertures **226** to communicate with the power bed **23**. The tubes **326** are free to vibrate up and down in response to the vibration input from the actuator **25'** during operation as there is a non-contact clearance around each vibrating tube **326**, actuator flange **225** and hopper bottom **123***f*. As before, the actuator **25'** can be configured to be substantially in-line with the dosing head **20** and one-directional. The actuator **25'** can apply the flow signal (e.g., flow energy) in a substantially vertical (only) direction. The flow signal/energy **28***s* can be applied so that the displacement is substantially all vertical but typically so that there is limited physical vertical displacement during the dispensing step. The actuator **25'** can be an in-line magnetostrictive actuator or any other suitable actuator or controllable vibrating member. In some embodiments, the actuator **25'** includes a plurality of, typically three, spaced-apart precision linear actuators that vibrate at least 3 points on a plane concurrently. For example, Model PI P/N S-9000002 actuator from PI (Physik Instrumente) L.P., Auburn, Mass. The stimulation or vibration motion can have a defined displacement profile, such as a non-harmonic displacement profile. The stimulation/vibration flow signal **28***s* can be generated in-line with a vertical axis associated with the dosing head ("A") so as to apply the flow energy so that the dosing head with a vertical displacement that is less than about 25 microns. As noted above, the target dose container member **30** can be closely spaced apart from a lowermost surface of the dosing head **20**, such as between about 20-100 microns, during filling.

The actuator **25'** can be configured to have a pre-load tensioning/compression to achieve a desired bipolar action in a dynamic mode. Actuator power wiring **25***p* can be provided via the top of the cylindrical body **25'** as shown in FIG. **25**A (but side or even bottom wiring (or wireless) may also be used).

As shown in FIG. **26**, an elastomeric gasket **140** can reside under the floor **123***f* and above the flange of the actuator **25'**. The gasket **140** can include an array of apertures **140***a* that align with the actuator flange apertures **226**. The gasket **140** is not a compression spring. An O-ring **142** can also be placed against the outer wall of the actuator cylinder and the hopper floor **123***f* to form a seal.

As shown in FIGS. **25**A, **25**B and **26**, the tube plate **325** has a planar upper surface **325***u* that holds the array of upwardly extending tubes **326** and this surface can be positioned to abut the flange actuator lower surface **225***b*. The tube plate **325** can also have a planar lower surface **325***b* that can be positioned to abut the top of the orifice plate **20***p*. The tubes **326** can be bonded, brazed, ultrasonically or metallurgically welded to the plate **325** or may be molded as a single-piece body or otherwise suitably formed. FIG. **25**B shows that the tube plate **325** can be aligned with flange apertures and the tubes **326** slidably advanced to attach the tube plate **325** to the actuator flange **225** (the gap space shown between the actuator flange lower surface **225***b* and the upper surface of the tube plate **325***u* is not the typical operative position). It is also noted that, in lieu of flange apertures, slots or other passages or flange shapes may be used to allow the tubes **326** to extend above the flange to communicate with the hopper bed **23**.

Bolts **27**, **227**, **327** can be used to releasably attach the tube plate **325**, the actuator flange **225**, the orifice plate **20** and/or the floor **123***f* together. However, in other embodiments, two or more of the components may be bonded, brazed, welded or otherwise be integrally attached together. It is contemplated that the assembly configuration used should be allow the tubes **326** to be free moving so as to not disrupt the vibration of the orifice plate/dosing head **20***p*, **20** and allow for uniformity of vibration over the ring of orifices in the dosing head/plate.

In some embodiments particularly suited for filling a dose disk with 60 dose containers in two concentric rows with the dose containers in each row having circumferentially offset centers, the tubular plate **325** can include 20 equally circumferentially spaced apart tubes **326** positioned at a common defined radial distance. The underlying orifice plate **20***p* can include 60 channels **20***ch* that align with 60 dose container apertures **30***c* for one dose disk **30** as described above (FIG.

1). As shown in FIG. **27**, each tube **326** can define a feed path **326***f* that can be equally spaced apart over a set of three closely spaced channels **20***ch* of the orifice plate **20***p* to feed dry powder concurrently to each of those three channels **20***ch*. The center of a respective feed tube **326** can reside above a triangle drawn by lines connecting the centers of each of the respective three channels **20***ch*.

In other embodiments, a single tube **326** can feed a single orifice plate channel **20***ch* or more than one tube **326** can feed a respective one channel **20***ch*. As noted above, the dose filling system **10'** may be configured to concurrently fill all dose containers **30***c* on a disk **30** or other configuration and the disk can include different numbers of dose containers **30***c*, such as 30 dose containers. The orifice dispensing channels **20***ch* can feed one or more underlying dose containers **30***c* or more than one channel **20***ch* can be used to fill an underlying dose container **30***c* as discussed above.

FIG. **10** illustrates different exemplary geometries for flow channels **20***ch*. The geometries include "straight" vertical flow channel geometries (with a suitable, very small size, orifice to avoid "free-flow" of the dry powder), funnel, inverse funnel, funnel to straight, funnel to angled and multiple angle changes over the length of the flow channel.

FIGS. **21-24** show examples of channels **20***ch* with different geometries. To be clear, although the channels **20***ch* are shown with respect to a dosing plate **20***p* with respect to different figures including FIGS. **21-24**, **5**A-**5**E, and **25**A-**25**B, the channel geometries are not required to be implemented using a plate **20***p* but instead can be included into other structures, members or components, including an integral dosing head. The plate **20***p*, where used, may, in some embodiments, have a diameter or cross-sectional length of about 70 mm and may include a lip **221** (FIG. **5**C). However, other shape and size plates may be used.

FIGS. **21**A-**21**D show about a 40 degree funnel angle with overlapping entry ports **20***a* and alternating inward and outward sloping channels **20***ch*. FIGS. **22**A-**22**C show a 60 degree funnel angle with overlapping entry ports **20***a* and alternating inward and outward sloping channels **20***ch*. FIGS. **5**D and **5**E show a 60 degree channel with all of the channels **20***ch* angled inward (and with an oval top entry port **20***a* with the long sides of the oval circumferentially oriented about the plate **20***p*. FIGS. **23**A-**23**B and **24**A-**24**E show a 30 degree funnel (with overlapping entry ports **20***a* and alternating inward and outward sloping channels **20***ch*). These figures also illustrate that the channels **20***ch* can define miniature hoppers which may help uniformly distribute powder **23** from the powder bed **23***b* into the channels **20***ch* and into the target receiving containers **30***a*.

FIGS. **21-24** also illustrate alternating inward and outward sloping channels **20***ch* with the upper portion of the channels having geometries configured to define overlapping entry ports **20***a* for at least two exit ports **20***e*, the upper portions of the channels **20***ch* a distance under the entry ports **20***a* merge into two respective exit ports **20***e* on front and back rows. The "crisscross" of downwardly sloping and narrowing funnels creates a shared upper collector bed that merges into lower isolated channel segments a distance down below the open top ports **20***a* toward (or even below) the middle portion. That is, the overlapping entry funnel shapes (shown as having semicircular outer perimeters) bifurcate into separate sloping lower channels **20***ch* at a location between about 30-80% of the channel length, typically between about 40-60% of the overall channel length (associated with the plate thickness) to angle in or out to feed adjacent pairs of inner and outer exit ports **20***e*. This creates a "mid-stage" powder bed that with vibration can provide a desired flow control and uniform powder distribution.

As shown in FIGS. **22**A-C, the channels **20***ch* have geometries and exit port sizes configured so as to have minimal or no direct powder path from the top **20***a* to the exit port **20***e*. That is, when looking down from the top as shown in FIG. **22**A, the exit port **20***p* is mostly, if not substantially entirely occluded from view. The exit port/orifice size can vary, but is typically less than about 1.8 mm, and more typically between about 1.2 mm-1.6 mm, for the limited or no "light" view path configuration.

FIG. **11** illustrates that the filling system **10** can be configured to accept interchangeable dosing plates **20***p* with different configurations of dosing channels **20***ch*. The control circuit **28** can be configured with a controller that has a library of "recipes" for selecting the corresponding operational parameters for generating the desired dose amounts of different dry powder formulations using the different dosing plates **20***p*. The dosing plates **20***p* can have an RFID or other electronic or optically readable data that identifies the plate type automatically.

FIGS. **12**A and **12**B illustrate examples of a filling system **100** with multiple sub-systems **10**. The sub-systems **10** can be in a row as shown in FIG. **12**A with the underlying dose container support members **30** provided in-line on a conveyor or other moving floor. A proximity sensor can be used to indicate when the dose containers **30***c* are in alignment with respective dosing channels **20***ch* and the vibratory flow signal **28***s* can be applied to fill the dose containers **30***c*. Each sub-system **10** can include its own powder bed **23** or, as shown, one line of the sub-systems includes a shared powder bed **23** and the other line includes another powder bed **23**. Other dose bed arrangements can be used, such as two dosing heads in one line sharing one bed, four dosing heads can share a single bed **23** (two from each line or four from one line) and the like.

FIG. **12**B shows that the sub-systems **10** can be closely spaced apart to overlie a circular holder with the containers **30**. The system **100** can include a single powder bed or multiple powder beds (not shown). The holder **40** can be mounted to a carousel that rotates to present different holders **40** with collections of empty members **30** to the dosing station for filling. A proximity sensor can be used to indicate when the dose containers **30***c* are in alignment with respective dosing channels **20***ch* and the vibratory flow signal **28***s* can be applied to fill the dose containers **30***c*.

The holder **40** can be configured to hold a plurality of dose container members **30** in alignment with each other and with the dose containers **30***c* in position for alignment with the corresponding dose channels **20***ch*. As shown in FIG. **12**C, the floor of each holder **40***f* can include a receiving channel **41** that matably engages the disk **30**. The holder **40** can also include tabs **40***p* that engage the alignments slots **34** for circumferential alignment.

FIG. **13** is an exemplary schematic of a filling system **100** that includes multiple dosing heads **20** and multiple transducers **25**. As shown, the system **100** includes a vibration flow signal circuit **28** that includes or communicates with a controller **128**. The controller **128** typically includes a digital signal processor and can include an HMI (Human Machine Interface) to allow a user to enter certain inputs. The controller **128** can include or communicate with a recipe module (computer program) **130**. The recipe module **130** can be programmed with an electronic library of defined operating parameters correlated to a particular dry powder or product (e.g., a product name, powder formulation and/or desired dose amount). The recipe module can provide the system **100**

with data regarding the proper setting of various components and allow the controller to implement these settings, e.g., vibration flow signal configuration, on/off time of the flow signal and, where used, the recipe can take into account a configuration of the dosing head for systems that allow for interchangeability of the dosing head **20** and/or dosing plate **20***p*.

The system **100** can also include proximity sensors **125** or other sensors that provide feedback on the position of the dose containers which can be electronically monitored to facilitate the timing of the on-off flow signal for automated filling.

FIG. **14** is an exemplary flow chart of a method that can be used to carryout embodiments of the invention. The method includes providing a dose container disk having upper and lower primary surfaces with a plurality of circumferentially spaced apart apertures associated with dose containers (block **200**). The dose container disk can be placed under a dosing head that resides below a dry powder bed, the dosing head having a plurality of circumferentially spaced apart dose filling channels with respective exit ports over the dose container disk so that the exit ports are aligned with the dose disk apertures (block **210**). A vibration flow signal is applied to the dosing head to cause the dry powder to concurrently flow out of the channels into the dose disk apertures (block **220**). The dose container disk is directly filled with a defined amount of dry powder in response to the applying step (block **230**). The applying step is ceased (abruptly or via a ramp down of the signal) to stop the flow of dry powder thereby filling a dose container disk with a defined amount of dry powder in each of the dose containers (block **240**). The ramp down of the signal may allow for a more controlled powder flow stoppage.

FIG. **15** is a block diagram of exemplary embodiments of data processing systems that illustrates systems, methods, and computer program products in accordance with embodiments of the present invention. The processor **410** communicates with the memory **414** via an address/data bus **448**. The processor **410** can be any commercially available or custom microprocessor. The memory **414** is representative of the overall hierarchy of memory devices containing the software and data used to implement the functionality of the data processing system **405**. The memory **414** can include, but is not limited to, the following types of devices: cache, ROM, PROM, EPROM, EEPROM, flash memory, SRAM, DRAM and magnetic hard drives.

As shown in FIG. **15**, the memory **414** may include several categories of software and data used in the data processing system **405**: the operating system **452**; the application programs **454**; the input/output (I/O) device drivers **458**; the vibratory signal generator module **450**; and the data **456**. The data **456** may include a plurality of dry powder data **451** corresponding to particular recipes with operating parameters for each dry powder or product, which may be obtained from an operator or stored by the dispensing system **420** and/or timing data that defines the meted dose amounts, flow rates, and flow signal "on" time for the dispensing port (allowing automatic control of the dispensing operation). As will be appreciated by those of skill in the art, the operating system **452** may be any operating system suitable for use with a data processing system, such as OS/2, AIX, OS/390 or System390 from International Business Machines Corporation, Armonk, N.Y., Windows CE, Windows NT, Windows95, Windows98, Windows2000, WindowsXP and WindowsVista, from Microsoft Corporation, Redmond, Wash., Unix or Linux or FreeBSD, Palm OS from Palm, Inc., Mac OS from Apple Computer, LabView, or proprietary operating systems. The I/O device drivers **458** typically include software routines accessed through the operating system **452** by the application programs **454** to communicate with devices such as I/O data port(s), data storage **456** and certain memory **414** components and/or the dispensing system **420**.

The application programs **454** are illustrative of the programs that implement the various features of the data processing system **405** and preferably include at least one application which supports operations according to embodiments of the present invention. Finally, the data **456** represents the static and dynamic data used by the application programs **454**, the operating system **452**, the I/O device drivers **458**, and other software programs that may reside in the memory **414**.

While the present invention is illustrated, for example, with reference to the signal generator module **450** being an application program in FIG. **15**, as will be appreciated by those of skill in the art, other configurations may also be utilized while still benefiting from the teachings of the present invention. For example, the module **450** may also be incorporated into the operating system **452**, the I/O device drivers **458** or other such logical division of the data processing system **405**. Thus, the present invention should not be construed as limited to the configuration of FIG. **15**, which is intended to encompass any configuration capable of carrying out the operations described herein.

The I/O data port can be used to transfer information between the data processing system **405** and the dispensing system **420** or another computer system or a network (e.g., an intranet and/or the Internet) or to other devices controlled by the processor. These components may be conventional components such as those used in many conventional data processing systems which may be configured in accordance with the present invention to operate as described herein.

While the present invention is illustrated, for example, with reference to particular divisions of programs, functions and memories, the present invention should not be construed as limited to such logical divisions. Thus, the present invention should not be construed as limited to the configuration of FIG. **15** but is intended to encompass any configuration capable of carrying out the operations described herein.

The flowcharts and block diagrams of certain of the figures herein illustrate the architecture, functionality, and operation of possible implementations of dry powder-specific dispensing and/or vibratory energy excitation means according to the present invention. In this regard, each block in the flow charts or block diagrams represents a module, segment, or portion of code, which comprises one or more executable instructions for implementing the specified logical function(s). It should also be noted that in some alternative implementations, the functions noted in the blocks may occur out of the order noted in the figures. For example, two blocks shown in succession may in fact be executed substantially concurrently or the blocks may sometimes be executed in the reverse order, depending upon the functionality involved.

In certain embodiments, the present invention can provide computer program products for operating a flowing dry powder dispensing system having channels **20***ch* and a vibration energy source associated therewith to facilitate controlled flow. The computer program product can include a computer readable storage medium having computer readable program code embodied in the medium. The computer-readable program code can include: (a) computer readable program code that a plurality of different vibration energy signals associated with a "recipe" that correlates the formulation to the dosing head/dosing plate geometry and/or dose container geometry; and (b) computer readable program code that directs the dispensing system to operate using the vibration energy signal for defined "on" and "off" times to dispense the desired dose amount (at the desired flow rate).

The invention will now be described in more detail in the following non-limiting example.

EXAMPLE

"On/off" flow control evaluation data was obtained using a laboratory system. To deliver the vibratory signal, the laboratory system included a harmonic signal drive configuration with a HP33120A function generator that can provide a carrier signal source connected to a timer (such as a Panasonic LT4H timer) to gate the drive signal, connected to a power amplifier connected to an electromagnetic (linear) actuator from Ling Dynamic Systems, model number V203. Preliminary results indicate relatively limited powder bed depth sensitivity, at least between about 3 mm to about 6 mm of initial bed depth. Powder bed depth for most trials was set to 6 mm and replenished if dropped below about 3 mm for a particular trial.

FIG. **16** is a graph showing flow channels with different geometries and no flow, flow with vibration and free flow limits with respect to channel outer diameter sizes (mm) and minimum displacement to cause flow for inh230 dry powder. The flow start/stop control with the plate vibration was observed for a range of about 0.4 mm displacement for 1.5 mm deep cylindrical channels. Flow start/stop with the plate vibration was observed at about 1.0 mm displacement for funnel shaped channels. It is noted that even at the minimum displacement threshold to induce flow through a channel, sporadic stopping of the flow sets the upper size limit of the channel. The OD (outer diameter) measurement was taken at the bottom of the plate, e.g., at the exit port/opening.

FIG. **17**A is a top perspective view of a plate **20***p* with about 41 degree funnel shaped channels **20***ch*. FIG. **17**B is a top perspective view of a plate **20***p* with about 30 degree funnel shaped channels **20***ch*. FIG. **17**C is a top perspective view of a plate **20***p* with substantially cylindrical (vertical) channels. FIG. **17**D illustrates flow of inh230 dry powder with hand tapping, no flow and free flow with respect to channel size (OD) measured at the exit port and geometry.

FIG. **18** is a graph of flow (mg/second) versus displacement (microns) for a 0.9 mm, 41 degree inverted funnel. The 0.9 mm measurement with respect to the funnel refers to the exit port (the smaller orifice of the funnel shape) and with respect to the inverted funnel refers to the entry port or orifice (also the smaller orifice of the "funnel" shape). As the displacement of the plate increased beyond the minimum threshold to induce flow, flow increases rapidly with displacement, then begins to decrease with further increases in displacement. Thus, smaller displacements can be more optimal for flow control and rate. This behavior may aid in selecting a vibration displacement operating point with reduced sensitivity of flow to displacement. It may be desirable to configure the vibration to cause displacement that is just under or approaching the peak flow.

FIG. **19** illustrates a minimum threshold displacement (microns/micrometers) to induce flow (at 300 Hz for Inh230) versus channel nominal outer diameter size (mm) (at the exit port) for three different channel geometries (cylindrical, taken at two different small sizes), and 30 and 41 degree funnels. Over the exit port diameter of interest, the displacement threshold has little variation.

FIG. **20**A is a graph of flow (mg/s) versus channel OD (nominal OD in mm at exit port) at minimum displacement for flow using a 300 Hz vibratory signal for Inh230.

FIG. **20**B is a graph of flow rate (mg/s) versus channel area (mm2) taken at the exit port for a 41 degree funnel. The target flow rate for sub-second filling operations of a dose ring or disk for Inh230 is shown as greater than 5 mg/s, typically between about 10-25 mg/s, which correlates to an opening size of about 2 mm^2 with about a 41 degree funnel channel geometry using the minimum displacement for flow and a flow signal of about 300 Hz. At the minimum displacement threshold, the 41 degree funnel geometry flow rate increase proportional to the area of the exit port.

The following exemplary claims are presented in the specification to support one or more devices, features, and methods of embodiments of the present invention. While not particularly listed below, Applicant preserves the right to claim other features shown or described in the application.

The foregoing is illustrative of the present invention and is not to be construed as limiting thereof. Although a few exemplary embodiments of this invention have been described, those skilled in the art will readily appreciate that many modifications are possible in the exemplary embodiments without materially departing from the novel teachings and advantages of this invention. Accordingly, all such modifications are intended to be included within the scope of this invention as defined in the claims. In the claims, means-plus-function clauses, where used, are intended to cover the structures described herein as performing the recited function and not only structural equivalents but also equivalent structures. Therefore, it is to be understood that the foregoing is illustrative of the present invention and is not to be construed as limited to the specific embodiments disclosed, and that modifications to the disclosed embodiments, as well as other embodiments, are intended to be included within the scope of the appended claims. The invention is defined by the following claims, with equivalents of the claims to be included therein.

That which is claimed is:

1. A method of filling a dose container disk, comprising:

providing a dose container disk having upper and lower primary surfaces with a plurality of circumferentially spaced apart apertures associated with dose containers;

placing the dose container disk under a dosing head that resides below a dry powder bed, the dosing head having a plurality of circumferentially spaced apart dose filling channels with respective exit ports over the dose container disk so that the exit ports are aligned with the dose container disk apertures;

applying a vibration flow signal to the dosing head for a defined time to cause dry powder from the dry powder bed to concurrently flow out of the exit ports of the dosing head dose filling channels directly into the dose container disk apertures; and

filling the dose container disk apertures with a defined amount of the dry powder in response to the applying step,

wherein the applied vibration is carried out using a vibration source that comprises at least one of the following:

(a) a plurality of actuators, one residing proximate each dosing channel to individually apply the flow signal to a respective channel;

(b) a single actuator that is configured to apply the flow signal to all of the dosing channels; or

(c) a plurality of actuators, at least one for sub-groupings of the dosing channels.

2. The method of claim **1**, wherein the vibration signal is a frequency modulated signal, and wherein the defined time of the applying step is less than about 1 second.

3. The method of claim **1**, wherein the dose container disk has at least 30 apertures, and wherein the dosing head has at least 30 dose filling channels, and wherein the filling step is carried out in less than 1 second.

4. The method of claim 1, wherein the dose container disk has about 60 apertures in two circular rows, and wherein the dosing head has at least about 60 dose filling channels with the exit ports arranged in two circular rows, and wherein the filling step is carried out in less than about 1 second.

5. A method of filling a dose container disk, comprising:

providing a dose container disk having upper and lower primary surfaces with a plurality of circumferentially spaced apart apertures associated with dose containers;

placing the dose container disk under a dosing head that resides below a dry powder bed, the dosing head having a plurality of circumferentially spaced apart dose filling channels with respective exit ports over the dose container disk so that the exit ports are aligned with the dose container disk apertures;

applying a vibration flow signal to the dosing head for a defined time to cause dry powder from the dry powder bed to concurrently flow out of the exit ports of the dosing head dose filling channels directly into the dose container disk apertures; and

filling the dose container disk apertures with a defined amount of the dry powder in response to the applying step,

wherein the dosing head is attached to a tube plate that includes an array of upwardly extending tubes that communicate with the dry powder bed, and wherein the applying step also causes the tubes to vibrate up and down to feed the dosing head channels.

6. A method of filling a dose container disk, comprising:

providing a dose container disk having upper and lower primary surfaces with a plurality of circumferentially spaced apart apertures associated with dose containers;

placing the dose container disk under a dosing head that resides below a dry powder bed, the dosing head having a plurality of circumferentially spaced apart dose filling channels with respective exit ports over the dose container disk so that the exit ports are aligned with the dose container disk apertures;

applying a vibration flow signal to the dosing head for a defined time to cause dry powder from the dry powder bed to concurrently flow out of the exit ports of the dosing head dose filling channels directly into the dose container disk apertures; and

filling the dose container disk apertures with a defined amount of the dry powder in response to the applying step,

wherein the applied vibration flow signal is generated using a vibration source that comprises a substantially cylindrical body actuator with a radially extending skirt having an array of circumferentially extending apertures extending therethrough.

7. A method of filling a dose container disk, comprising:

providing a dose container disk having upper and lower primary surfaces with a plurality of circumferentially spaced apart apertures associated with dose containers;

placing the dose container disk under a dosing head that resides below a dry powder bed, the dosing head having a plurality of circumferentially spaced apart dose filling channels with respective exit ports over the dose container disk so that the exit ports are aligned with the dose container disk apertures;

applying a vibration flow signal to the dosing head for a defined time to cause dry powder from the dry powder bed to concurrently flow out of the exit ports of the dosing head dose filling channels directly into the dose container disk apertures; and

filling the dose container disk apertures with a defined amount of the dry powder in response to the applying step,

wherein the dosing head resides under a tube plate with an array of upwardly extending tubes having upper and lower ends positioned so that upper ends of the tubes are in communication with dry powder in the dry powder bed and lower ends of the tubes reside proximate the dosing head dose filling channels, and wherein the filling is carried out to flow dry powder from the dry powder bed, then through the tubes to the dosing head filling channels.

8. The method of claim 1, wherein the dosing head has at least 60 channels with the exit ports arranged in at least two substantially circular rows, and wherein the exit ports have a diameter of about 3 mm or less.

9. The method of claim 1, wherein the dosing head filling channels have a geometry that defines a miniature-hopper that holds a plurality of bolus amounts of dry powder, wherein the geometry and vibration flow signal are selected to provide an ON OFF flow pattern for a respective dry powder formulation to deliver a defined dose amount in the range of between about 0.5-15 mg in less than about 1 second, and wherein the dry powder bed resides in an unsealed, non-pressurized housing.

10. A method of filling a dose container disk, comprising:

providing a dose container disk having upper and lower primary surfaces with a plurality of circumferentially spaced apart apertures associated with dose containers;

placing the dose container disk under a dosing head that resides below a dry powder bed, the dosing head having a plurality of circumferentially spaced apart dose filling channels with respective exit ports over the dose container disk so that the exit ports are aligned with the dose container disk apertures;

applying a vibration flow signal to the dosing head for a defined time to cause dry powder from the dry powder bed to concurrently flow out of the exit ports of the dosing head dose filling channels directly into the dose container disk apertures; and

filling the dose container disk apertures with a defined amount of the dry powder in response to the applying step,

wherein the dosing head resides under a substantially circular tube plate with an array of circumferentially spaced apart tubes, wherein the dosing head has a body that is defined by a substantially circular orifice plate that includes at least one row of circumferentially spaced apart elongate channels, and wherein the applied vibration is carried out using a vibration source that includes an actuator with a substantially cylindrical body with a vertically extending centerline aligned with a vertical linear vibration axis of the orifice plate, the actuator having a radially extending skirt that is attached to the orifice plate and the tube plate, and wherein the actuator comprises a plurality of linear actuators that cause the tubes to vibrate in a vertical direction to feed dry powder to the orifice plate and to apply the vibration signal to the orifice plate.

11. A method of filling a dose container disk, comprising:

providing a dose container disk having upper and lower primary surfaces with a plurality of circumferentially spaced apart apertures associated with dose containers;

placing the dose container disk under a dosing head that resides below a dry powder bed, the dosing head having a plurality of circumferentially spaced apart dose filling

channels with respective exit ports over the dose container disk so that the exit ports are aligned with the dose container disk apertures;

applying a vibration flow signal to the dosing head for a defined time to cause dry powder from the dry powder bed to concurrently flow out of the exit ports of the dosing head dose filling channels directly into the dose container disk apertures; and

filling the dose container disk apertures with a defined amount of the dry powder in response to the applying step,

wherein the dosing head channel exit ports are arranged in first and second rows of substantially concentric circles, wherein the first row of exit ports have radially extending centerlines that are offset circumferentially from radially extending centerlines of the second row of exit ports, and wherein the channels are configured to have alternating inwardly and outwardly sloping channel walls.

12. The method of claim **11**, wherein an exit port on the first row and a neighboring exit port on the second row define respective pairs of adjacent exit ports, and wherein corresponding entry ports of the pairs of exit ports overlap so that dry powder flows from a respective entry port to a corresponding pair of adjacent exit ports during the filling step.

13. A method of filling a dose container disk, comprising:

providing a dose container disk having upper and lower primary surfaces with a plurality of circumferentially spaced apart apertures associated with dose containers;

placing the dose container disk under a dosing head that resides below a dry powder bed, the dosing head having a plurality of circumferentially spaced apart dose filling channels with respective exit ports over the dose container disk so that the exit ports are aligned with the dose container disk apertures;

applying a vibration flow signal to the dosing head for a defined time to cause dry powder from the dry powder bed to concurrently flow out of the exit ports of the dosing head dose filling channels directly into the dose container disk apertures; and

filling the dose container disk apertures with a defined amount of the dry powder in response to the applying step,

wherein the applied vibration is carried out using at least one vibration source in communication with the dosing head channels configured to controllably apply a vibration flow signal, wherein, in use, the vibration flow signal is applied to the dosing head Channels for a defined time so that dry powder from the dry powder bed flows through the elongate channels and out the exit ports in a defined dose amount, and when the vibration flow signal is removed from the dosing head channels, dry powder does not flow out of the exit ports,

wherein the dry powder bed comprises a dry powder having a pharmaceutically active agent, and wherein the agent comprises one or more of the following bronchodilators:

albuterol, salmeterol, ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, terbutaline, isoetharine, tulobuterol, or (−)-4-amino-3,5-dichloro-α-[[6-[2-(2-pyridinyl)ethoxy]hexyl]methyl] benzenemethanol, wherein the bronchodilator may be used in the form of salts, esters or solvates to thereby optimize the activity and/or stability of the medicament.

14. A method of filling a dose container disk, comprising:

providing a dose container disk having upper and lower primary surfaces with a plurality of circumferentially spaced apart apertures associated with dose containers;

placing the dose container disk under a dosing head that resides below a dry powder bed, the dosing head having a plurality of circumferentially spaced apart dose filling channels with respective exit ports over the dose container disk so that the exit ports are aligned with the dose container disk apertures;

applying a vibration flow signal to the dosing head for a defined time to cause dry powder from the dry powder bed to concurrently flow out of the exit ports of the dosing head dose filling channels directly into the dose container disk apertures; and

filling the dose container disk apertures with a defined amount of the dry powder in response to the applying step,

wherein the dosing head comprises at least one plate that defines at least some of the channels, wherein the dosing head is configured to releasably engage different plates having different channel geometries, and wherein the method further comprises interchanging one plate for a different plate with different channel geometries to carry out the filling step for different target dose container disks.

15. A method of filling a dose container disk, comprising:

providing a dose container disk having upper and lower primary surfaces with a plurality of circumferentially spaced apart apertures associated with dose containers;

placing the dose container disk under a dosing head that resides below a dry powder bed, the dosing head having a plurality of circumferentially spaced apart dose filling channels with respective exit ports over the dose container disk so that the exit ports are aligned with the dose container disk apertures;

applying a vibration flow signal to the dosing head for a defined time to cause dry powder from the dry powder bed to concurrently flow out of the exit ports of the dosing head dose filling channels directly into the dose container disk apertures; and

filling the dose container disk apertures with a defined amount of the dry powder in response to the applying step,

wherein the dosing head dose filling channels communicate with dry powder in the dry powder bed to define miniature hoppers that each hold a plurality of bolus amounts of dry powder, and wherein the filling step is carried out in response to the applying step to controllably directly dispense a single bolus amount to an aligned dose container in response to an on and off application of the vibration flow signal to the dose filling channels.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 9,278,767 B2
APPLICATION NO. : 14/221648
DATED : March 8, 2016
INVENTOR(S) : Meckstroth et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Specification:
Column 18, Line 9: Please correct "S-9000002" to read -- S-900C002 --

In the Claims:
Column 27, Claim 13, Line 48: Please correct "Channels" to read -- channels --

Signed and Sealed this
Thirteenth Day of September, 2016

Michelle K. Lee

Michelle K. Lee
Director of the United States Patent and Trademark Office